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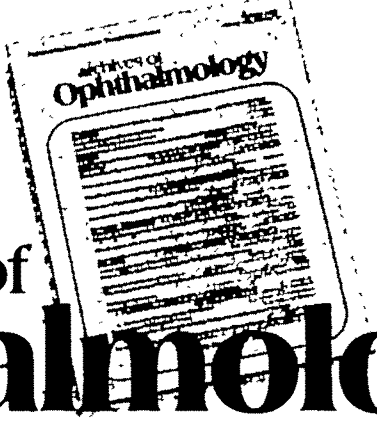

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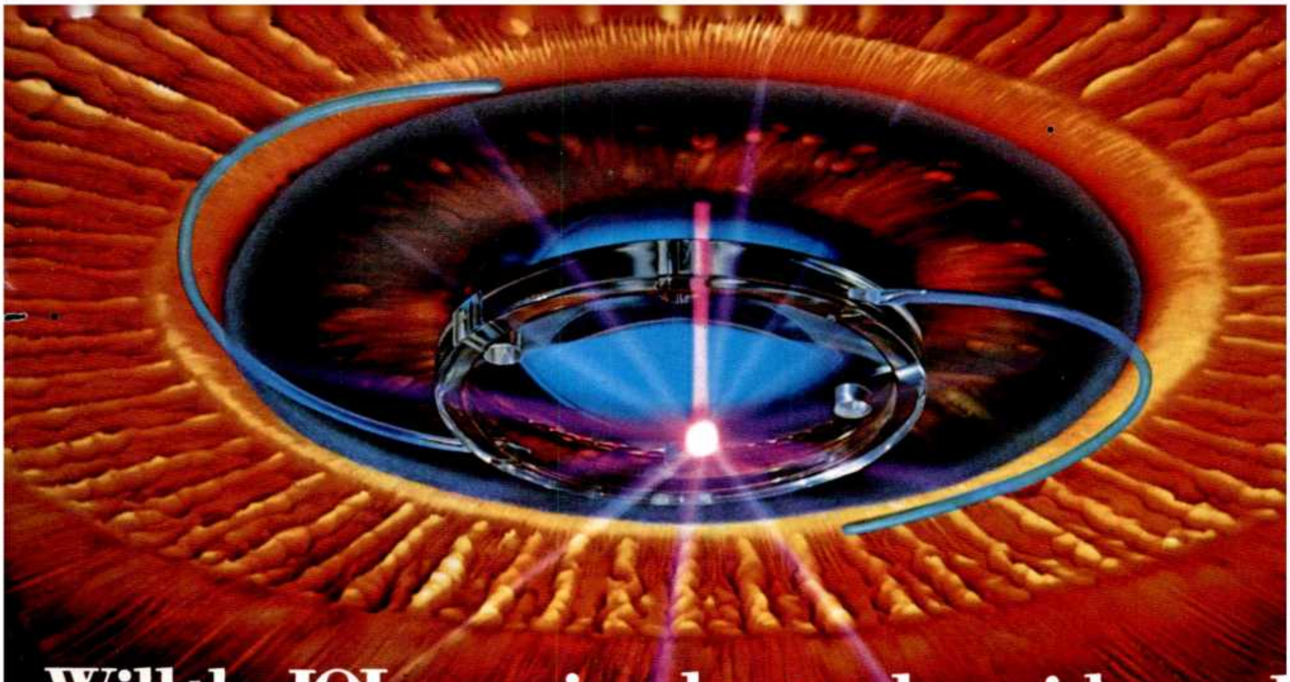

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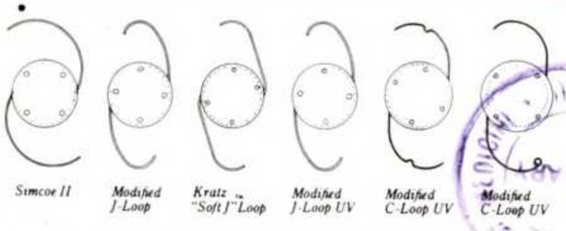

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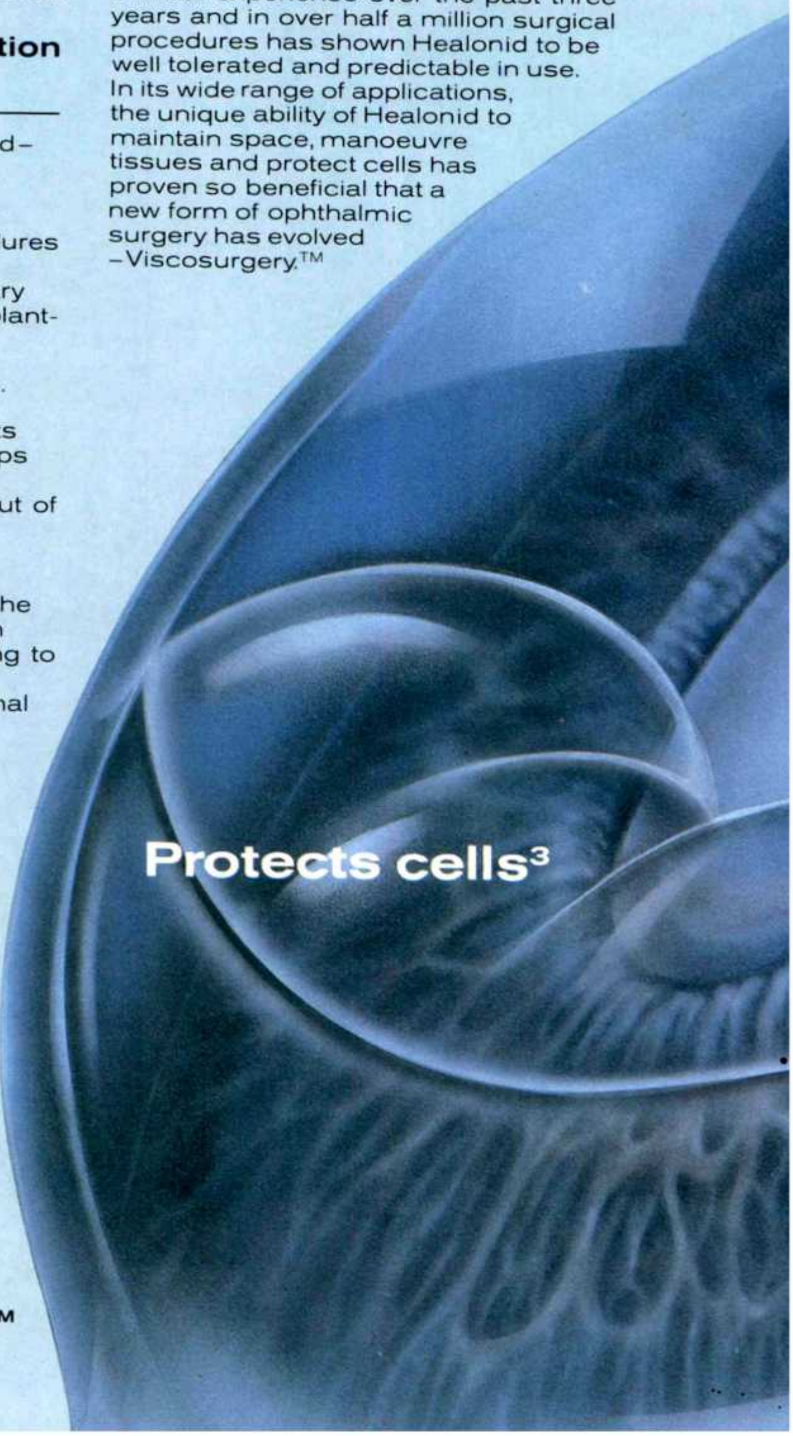

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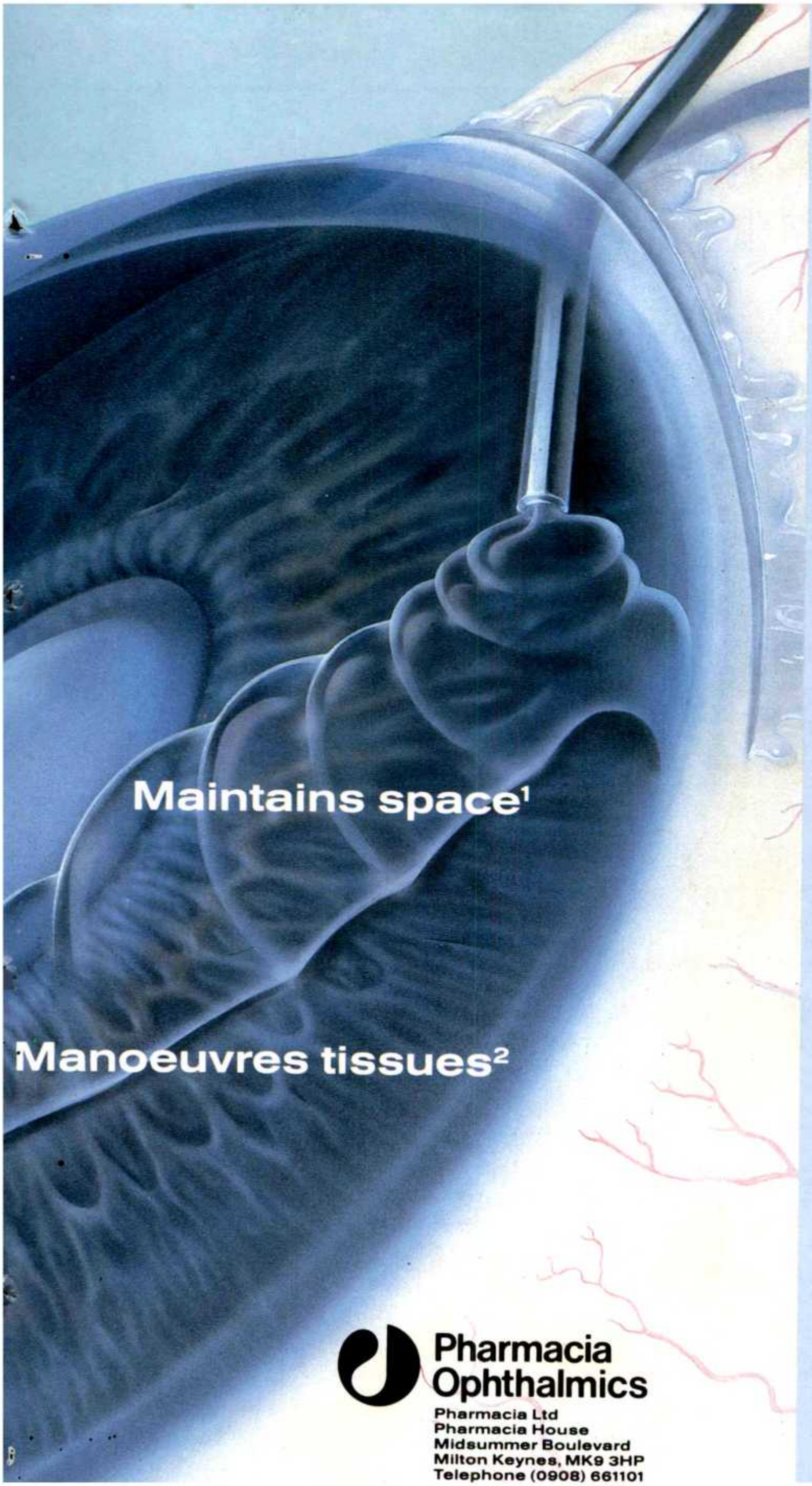

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INDICATIONS
Surgical procedures on the eye, including intraocular lens insertion, intra and extra capsular lens extraction, glaucoma surgery, corneal graft, surgery for accidental trauma retinal detachment and vitreal replacement procedures.

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PRECAUTIONS
The anterior chamber should not be over-filled with HEALONID, except in glaucoma surgery. At close of surgery some of the HEALONID should be removed by irrigatior or aspiration. Intraocular pressure should be monitored during the post operative period and any excessive rises treated with appropriate therapy.

CONTRA-INDICATIONS, WARNINGS
There are no known contra-indications to HEALONID. Because the drug is extracted from avian tissues, despite rigorous purification procedures minute amounts of protein are present, and thus the remote possibility of idiosyncratic reactions remains.

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The drug is very well tolerated and the only untoward effect reported has been a transier rise in intraocular pressure in a few cases.

PHARMACEUTICAL PRECAUTIONS
Store at 2-8°C protected from light and freezing. Shelf life 3 years.

LEGAL CATEGORY POM.

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FURTHER INFORMATION
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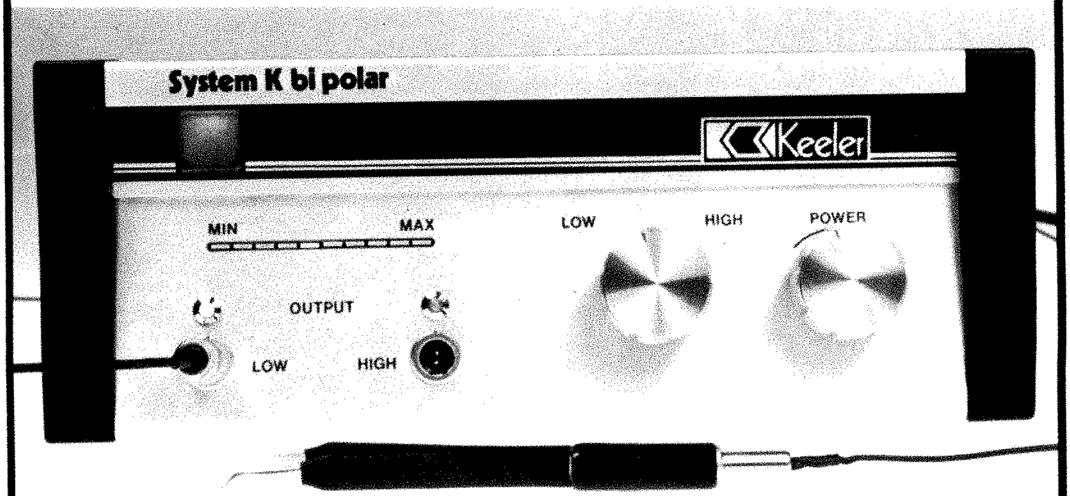

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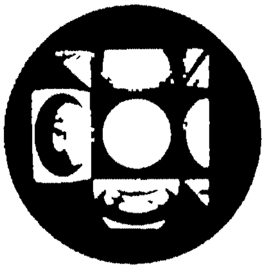

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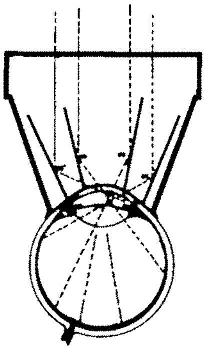

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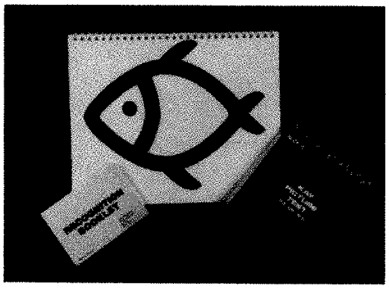

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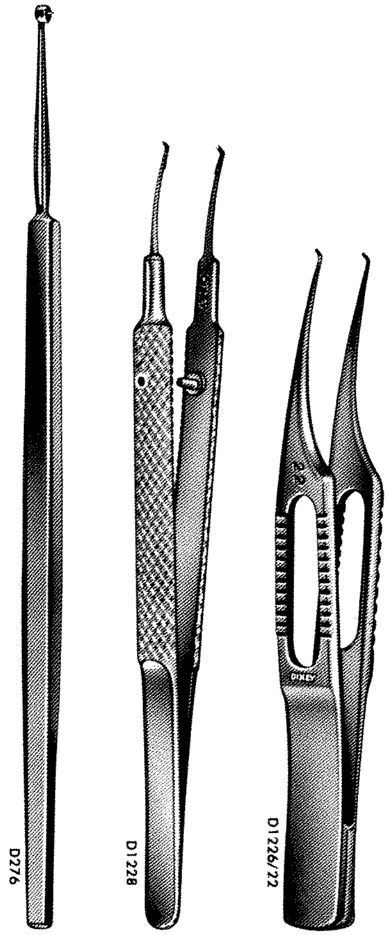

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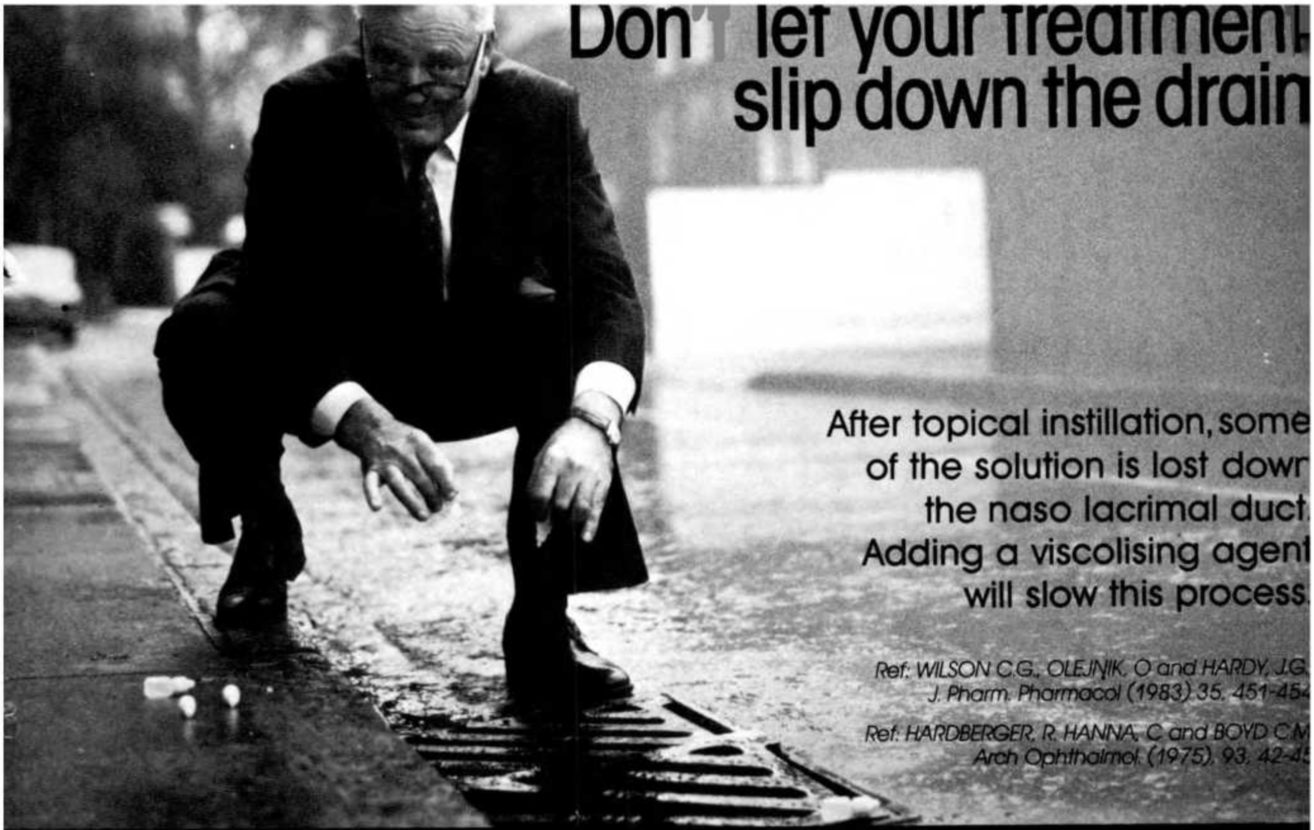

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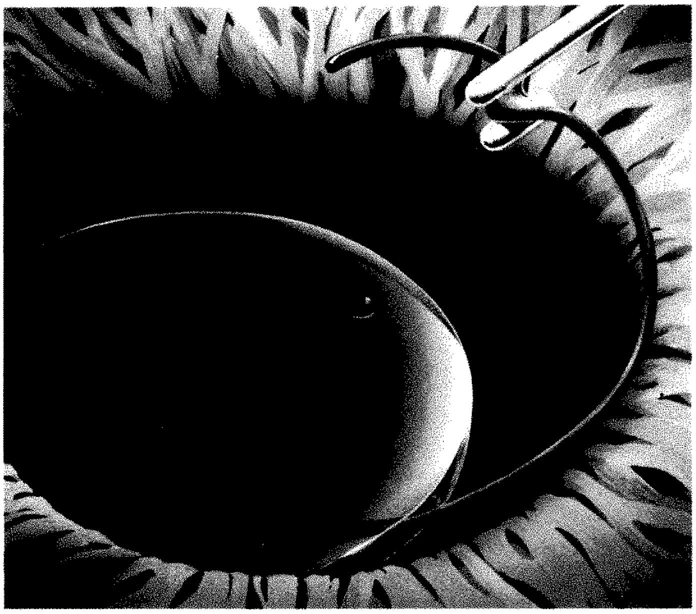

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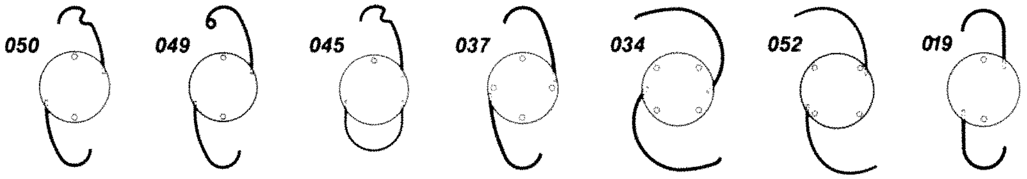

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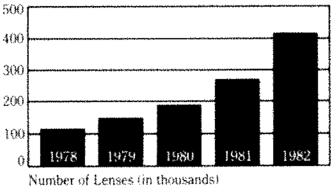

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References:

1. Garner LL, et al, Amer. J. Ophthalmol. 1963 **55,** 323-327.
2. Duke Elder, WS, Textbook of Ophthalmology as quoted in: Moses, RA, Adler Physiology of the Eye, 1975: 192.

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British Journal of Ophthalmology, 1985, **69**, 477–481

On the nature and the role of the subsurface vesicles in the outer epithelial cells of the conjunctiva

P N DILLY

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SUMMARY The layer of the tear film in contact with the conjunctiva is mucus. This mucus comes from two sources, the conjunctival goblet cells and the subsurface vesicles. These vesicles are found just below the surface of the conjunctival cells. They contain long chain mucus glycoprotein molecules that are joined to the vesicle membrane. The vesicles fuse with the surface membrane of the conjunctival cells and expose their mucus glycoprotein chains to the overlying mucus. Chemical and physical bonds between the two types of mucus help to bind the mucus layer to the conjunctiva. The vesicle membrane becomes incorporated in the cell membrane and supplies the membranes for the microvilli that cover the exposed surface.

The existence of membrane bound vesicles just below the cell membrane of the exposed surfaces of the outer layer of cells of the conjunctiva has been known for some time. They were first described by Wanko *et al.* in 1964[1] from the perilimbal zone of the human conjunctiva. Takakusaki[2] noted that the number of subsurface vesicles increased in vernal conjunctivitis and suggested that this was a pathological change. Srinivasan *et al.*[3] found a similar increase in subsurface vesicles of the conjunctiva associated with a methyl methacrylate ocular prosthesis. Greiner *et al.*[4] proposed that these vesicles were a second mucus secretory system of the human conjunctiva in addition to the well established conjunctival goblet cell source. Greiner *et al.*[5] on the basis of toluidine blue staining and periodic acid Schiff (PAS) reactions demonstrated that the vesicle content was probably a mucoprotein in giant papillary conjunctivitis associated with hard contact lenses. He showed that the vesicle contents were discharged on to the surface of the eye. Greiner and Allansmith[6] showed that the number of subsurface vesicles increased in contact lens wearers. Dilly and Mackie[7] showed that the number of vesicles was increased in the anaesthetic conjunctiva. Using a modified Thiéry's method[8] as a specific stain for mucoprotein, they confirmed Greiner and colleagues'[4-6] conclusion as to the mucoprotein nature of the content of the subsurface vesicles.

Materials and methods

With the informed consent of sufferers from external eye disease and persons with normal eyes human conjunctival biopsy specimens were taken from the lower lids with a 2 mm Elliott trephine. These specimens were fixed in glutaraldehyde. Similar larger biopsy specimens were taken immediately post mortem from a series of apparently normal eyes. These too were fixed in glutaraldehyde. They were processed for electron microscopy either by ruthenium red staining, tannic acid combined with ruthenium red, or by Thiéry's method.[8] The specimens were embedded in 'Spurr' resin. Sections were cut with a Sorvall ultramicrotome, mounted on gold grids, and examined in a Phillips 301 transmission electron microscope.

Results

Besides these conditions, where there was an increase in number of subsurface vesicles,[4-7] we have found in late stages of keratoconjunctivitis sicca a complete absence of vesicles.

The vesicles themselves varied in size from about 50 nm to 100 nm in diameter. They were usually circular or somewhat oval in profile. The vesicles might be more than one row deep beneath the cell membrane (Fig. 1).

Greiner *et al.*[5] described the vesicles as single membrane bound. My results suggest that they are

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bounded by a double membrane very similar in structure to the cell surface membrane. This double membrane is easy to miss, because the nature of a spherical vesicle is that little of the surrounding membrane will be 'end on' to the electron beam and so be resolved as a unit membrane. However, by tilting the section in the electron beam until optimum alignment of the vesicle was achieved the unit membrane nature of the vesicle wall could be resolved (Fig. 2).

Specialised electron microscope staining for mucus glycoprotein by Thiéry's[8] silver method showed that the subsurface vesicles contain a mucoprotein (Figs. 3, 4). Ruthenium red staining confirmed these results.

An interesting and revealing finding was that there are identical staining reactions associated with the surface membrane of the epithelial cells of the conjunctiva (Figs. 3, 4). Apart from a few ribosomes within the epithelial cell cytoplasm these were the only two sites in the conjunctival epithelium where such a staining reaction took place.

Closer examination revealed that the reaction product of the staining was associated with the innermost membrane layer of the vesicles and the outermost layer of the cell membrane (Fig. 2). This staining was not spread evenly throughout the membrane. It occurred in punctate masses separated by bits of unstained membrane (Figs. 3, 5). These staining sites were evenly spaced on the membrane surface. This observation suggests that the mucus glycoprotein of the subsurface vesicles and of the surface layer of the epithelial cells was bound to specific sites in the cell membrane. The distribution on the cell surface was similar to that on the inner wall of the vesicle membrane (Fig. 4).

In sections stained with Thiéry's method[8] there were chains of silver granules extending from these binding sites. Similar chains were found after iron haematoxylin staining. Such chains were found extending both from the wall of the subsurface vesicle into the cavity of the vesicle (Fig. 4) and out from the surface membrane of the epithelial cell into the overlying layer of mucus that came from the conjunctival epithelial goblet cells (Fig. 4).

The chains of silver granules branched and spread out in three dimensions from the binding sites. Such branching chains increased the area covered by the side chains and the amount of chain in contact with the goblet cell mucus.

Vesicles with similar staining properties to the subsurface vesicles were found in close association with the channels of endoplasmic reticulum and Golgi complex. There appeared to be an increase in the amount of Golgi complex in those cells that had an increased number of subsurface vesicles. Such observations suggest that the vesicles and their contents were produced by the endoplasmic reticulum and modified by the Golgi complex before they achieved the subsurface site. There was a considerable array of cytoskeletal elements in the cytoplasm just below the exposed surface of the epithelial cells (Fig. 2). It was probably these elements that guided the vesicles to their position beneath the membrane and finally their fusion with the membrane. The cytoskeletal elements probably also supported the cell membrane and helped to disperse the load exerted upon it by the tethered mucus.

Discussion

The subsurface vesicles appear to be a source of mucus with a very specific function. The role of the subsurface vesicle mucus is to anchor the goblet cell mucus to the surface membranes of the epithelial cells covering the eye. The mucus the vesicles contain is bound to the vesicle membrane and has long chains. When the subsurface vesicles fuse with the cell membrane of the epithelial cells and become in-

Fig. 1 *Low power electron micrograph showing a healthy cell in the outermost layer of the conjunctival epithelium that contains a layer of subsurface vesicles beneath its microvillous border. (×5600).*

Fig. 2 *Details of the surface membrane, and subsurface vesicle membrane showing that the staining is confined to one leaflet of the unit membrane. (×60 000).*

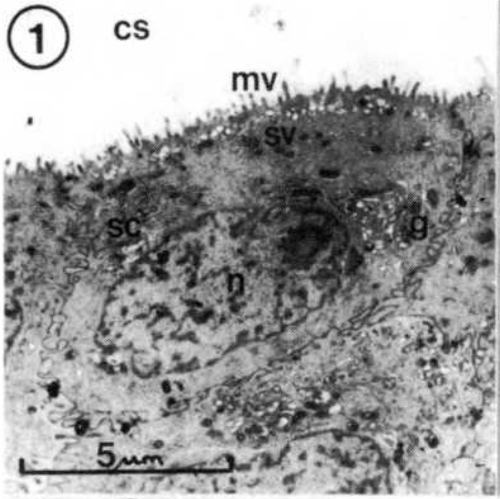
Fig. 3 *Silver stained electron micrograph showing the similarity in staining properties between the subsurface vesicle contents and the masses associated with the microvilli. (×32 500).*

Fig. 4 *Electron micrograph showing the mucus glycoprotein chains extending out from the microvillous surface, as well as others within the subsurface vesicles. (×81 400).*

Fig. 5 *High-power electron micrograph showing that the distribution of stain on the microvillous surface is not uniform but is distributed in evenly spaced clumps. (×75 000).*

Fig. 6 *A diagram to illustrate the way that the subsurface vesicle fuses with the cell membrane and thus exposes its contents to the mucus secreted by the goblet cells.*

Abbreviations:
cs = *External surface of conjunctiva, the site of the tear film.*
ds = *Densely staining anchor site, where the mucus glycoprotein is attached to the microvillous membrane.*
f = *Filamentous cytoskeletal elements.* g = *Golgi apparatus.*
gm = *Goblet cell mucus.* mc = *Mucous glycoprotein chain.*
mv = *Microvillus.* n = *Nucleus.* sc = *Surface cell of the conjunctival epithelium.* sv = *Subsurface vesicle.*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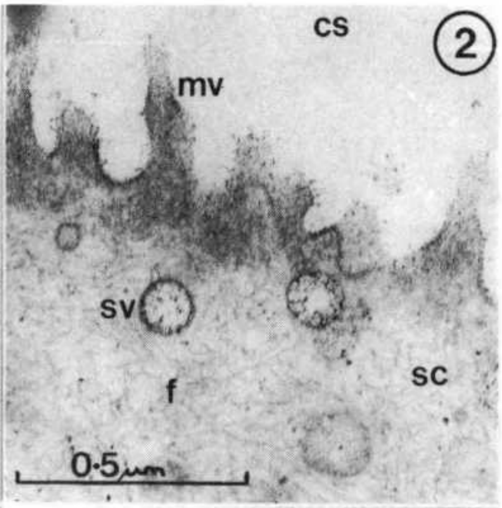
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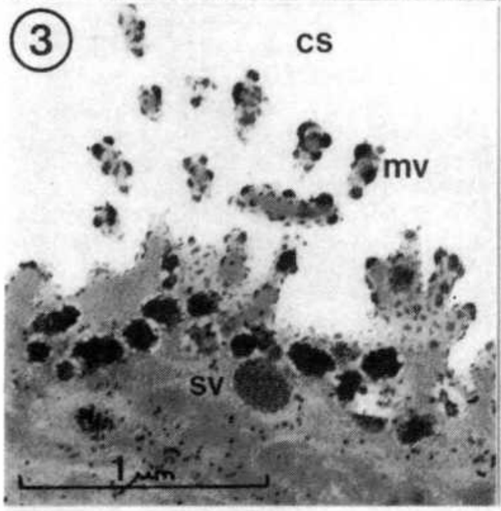
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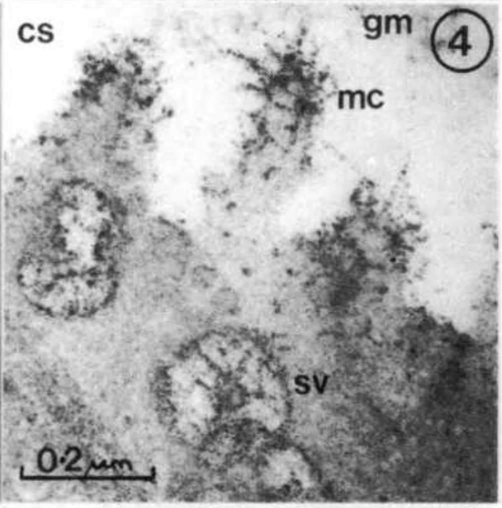
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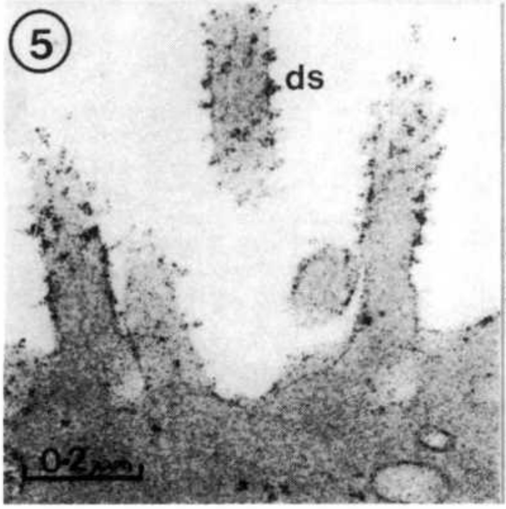
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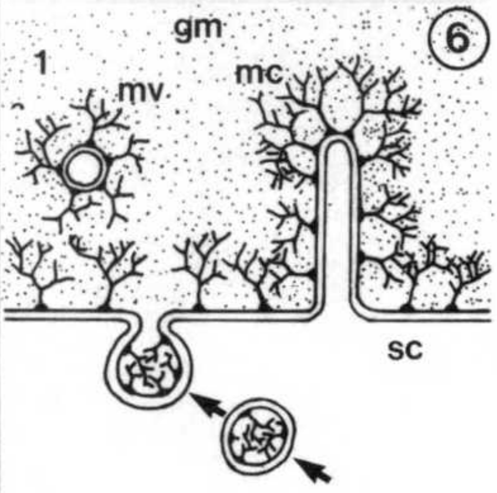
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corporated into the cell surface, these chains extend outwards into the mucus layer covering of the surface (Fig. 6). This covering layer of mucus is secreted by the goblet cells within the conjunctival epithelium. The intermingling of the mucus glycoprotein chains with mucus mechanically and probably chemically bonds the mucus layer to the surface of the eye and increases its adhesion to the conjunctival surface. Any such increase in adhesion will resist the cohesive forces of the tear film and thus oppose break up of the tear film.

The increase in numbers of subsurface vesicles that occur in some external eye diseases may reflect an attempt to increase the binding of the mucus to the eye surface. There is of course the alternative explanation that these vesicles are inhibited in some way from discharging their contents and so have accumulated beneath the surface.

One can propose the hypothesis that there is some factor in normal tear secretions that acts on the superficial cells causing the submembrane vesicles to be released. In normal eyes there is a balance between vesicle release and vesicle production, and thus vesicles do not accumulate under the cell surface membrane. Whereas in the diseased state this balance is upset. Such an upset could either be in the composition of the tear film—say a reduction in the potency or amount of a vesicle releasing agent—or a change in the surface cells themselves. Evidence that such a mechanism might exist and the nature of the releasing agent comes from the work of Meier and Hay,[9] who showed that there was stimulation of extracellular matrix synthesis in the developing cornea by glycosaminoglycans.

There is no doubt that in the diseased eyes I have examined some of the subsurface vesicles do fuse with the surface membrane and produce apparently normal anchoring chains. It is probable therefore that the vesicles and their contents are normal and that the fault in the anchoring system lies elsewhere, probably in the control of their fusing with the external cell membrane. In late keratoconjunctivitis sicca, however, the subsurface vesicles are absent.

When the subsurface vesicles fuse with the cell membrane, a considerable amount of extra surface membrane becomes available to the cell. This incorporated subsurface vesicle membrane is probably the source of the cell membrane of the microvilli that sprout on the exposed surface of the epithelial cells, microvilli are not found on the surfaces of the deeper cells in the epithelial cell layers.

The production of microvilli from the subsurface vesicles would also explain the varying sizes, shapes, and form of microvilli found on the differing cells at the surface. These changes in morphology may represent different stages in maturity of the microvilli. It is known that when new cells reach the surface only a small part of their membrane is exposed initially, and that it bears a different size and density of microvilli from the more mature cells around it.[10] This suggests that the process is triggered by the cell reaching the surface, and, since only a small area of cell surface is exposed initially, the demands upon the cell to produce microvilli will be less than if the whole surface were exposed at once.

The nature of the membrane binding site has not been determined. The molecular link might be the lipophilic part of the mucus glycoprotein. It is interesting to speculate, however, that they might be lectins. Lectins are carbohydrate-bonding proteins that have two critical properties, specificity for a particular sugar residue and bivalency or polyvalency. They are usually subdivided on the basis of whether or not they integrate into membranes. The non-membrane lectins are soluble. The integral membrane lectins appear to have evolved to bind glycoconjugates to membranes either at the cell surface or within vesicles. This is the role that the binding agent has to perform in the epithelial surface of the eye. There is experimental support for the function of integral membrane lectins in the endocytosis of glycoproteins and in cellular translocation. So perhaps it is not too much to assume a similar role in exocytosis. There is also evidence that the major function of soluble lectins is to bind the complementary glycoconjugates on and around the cells that release them. Since both the lectins and the glycoconjugates may be multivalent, large macromolecular complexes that shape the extracellular environments may be formed. Immunohistochemical studies suggest that there is secretion of soluble lectins.[11]

We have here not only a mechanism that would bind that mucoprotein secreted by the subsurface vesicles to the cell membrane, but also a mechanism that would bind the mucus from other sources, especially the goblet cells, to the anchored mucoprotein.

Such an anchoring system must be very vulnerable to changes in the state of the conjunctival cells. Any form of squame formation, modification of the metabolism, or death of the surface cells would probably modify the production of subsurface vesicles and their ability to fuse with the cell membrane to fulfil their anchoring role. Such an anchoring role is vitally important in keeping the eye wet, because the cohesive force of tear fluid is greater than that of the naked conjunctiva, and it is the 10 or so dynes per cm contributed by these adhesive links that increase the adhesive forces of the conjunctival surface sufficiently to promote tear film spreading across the conjunctiva and to achieve all-over wetting of the surface vital for a healthy eye.

The role of the surface microvilli and the binding chains is essentially similar: they both stop the most adjacent layer of mucus moving. It is probable that the turbulence induced by the microvilli will stop the flow of mucus around them, and the chains of mucus glycoprotein will extend their effect. Their effect will be that the tear flow will be much greater near the surface of the film than near its epithelial interface.

The role of the goblet cell mucus is probably one of lubricating the movement of the eyelid. And having its innermost layers anchored will ensure that the breaking of the mucus-layer shear forces induced by lid movements will occur well clear of the cell surface. This will protect the epithelial cells from damage by movements of the lid.

A reduction in the effectiveness of subsurface vesicle mucus-glycoprotein binding, however caused, will reduce the adhesive forces holding the goblet cell mucus to the eye surface. Such a reduction will allow movement of the mucus, reduce the thickness protecting the epithelial cells, and ultimately contribute to a more rapid tear film break up.

I thank Mr Ian Mackie, FRCS, for enthusiastic support, Miss C Cope for dedicated technical expertise, and Mrs M Coulton for typing.

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Indications for vitrectomy in congenital retinoschisis

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SUMMARY Two patients with congenital retinoschisis developed rhegmatogenous retinal detachments with either a tractional component or associated vitreous haemorrhage. The second patient also had a large, raised schisis cavity under vitreous traction, which obscured visualisation of the macula. Vitrectomy is indicated for some patients with congenital retinoschisis.

Congenital retinoschisis, a relatively rare ocular disorder[1] first described by Haas[2] in 1898, has also been called congenital vascular veils,[3] cystic disease of the retina in children,[4] juvenile retinoschisis,[5] and inherited retinal detachment.[6] Usually bilateral,[7] the disorder is inherited as an X-linked Mendelian recessive trait affecting males,[8-10] though a few sporadic cases have been reported in females.[11]

Retinoschisis has a predilection for the inferotemporal quadrant[7] and rarely extends to the ora serrata. Large blood vessels frequently course through the inner retinal wall, and other vascular elements may traverse the schisis cavity.[12] Retinal holes in the inner layer are common and usually appear in multiples.[13]

Other ocular changes reported in retinoschisis include neovascular glaucoma,[14] optic atrophy,[4 15] and diminished visual acuity[16] secondary to foveal dystrophy. Conway and Welsh[12] described the presence of a haemorrhagic retinal cyst surrounded by exudate extending into the macula.

Retinal detachment is a serious complication associated with congenital retinoschisis.[4 7 13 17 18] Surgical treatment in the past has involved conventional scleral buckling procedures. The use of vitrectomy to remove vitreous haemorrhage and to repair a retinal detachment with a tractional component in patients with X-linked retinoschisis is, to the best of our knowledge, described for the first time here.

Case reports

CASE 1

An 11-year-old boy, who was diagnosed as having X-linked retinoschisis at age 5, was referred to the University of Illinois Eye and Ear Infirmary with a retinal detachment in his right eye. He was the product of a normal pregnancy and had no congenital anomalies Two older brothers also had X-linked retinoschisis. An ocular examination of his mother and three of his sisters was unremarkable. No consanguinity existed between the parents. When the patient was 4 years old, an electroretinogram (ERG) (performed with the patient under anaesthesia) showed an extinguished B wave. The boy's two brothers had similar ERG changes.

Ocular examination revealed a corrected vision of counting fingers at 6 feet (1·8 m) in the right eye and 5/200 in the left eye. External examination revealed 8° of left esotropia. Biomicroscopy was unremarkable. Ophthalmoscopy of the left eye revealed a large grey intravitreal membrane floating in the inferior vitreous between the inferior arcade and equator. The macula was distorted, and inferiorly a retinoschisis cavity was observed. A fundus examination of the right eye disclosed cystic macular changes. A full-thickness retinal detachment (Fig. 1) that involved the macula and most of the inferior retina extended from the 4 to 8 o'clock meridians. A small schisis cavity was noted in the inferior retina near the equator. Another area of retinoschisis was present inferior to the temporal arcades. A vitreous veil exerted traction on a retinal fold along the inferotemporal arcade. A partial-thickness retinal tear was also present below the retinal fold.

During surgery the partial-thickness retinal tear inferior to the macula was noted to be under considerable vitreous traction. The vitreous band was transsected with a bipolar[19] cautery attached to the fiberoptic membrane dissector and vitrophage to allow the underlying retina, including the partial-

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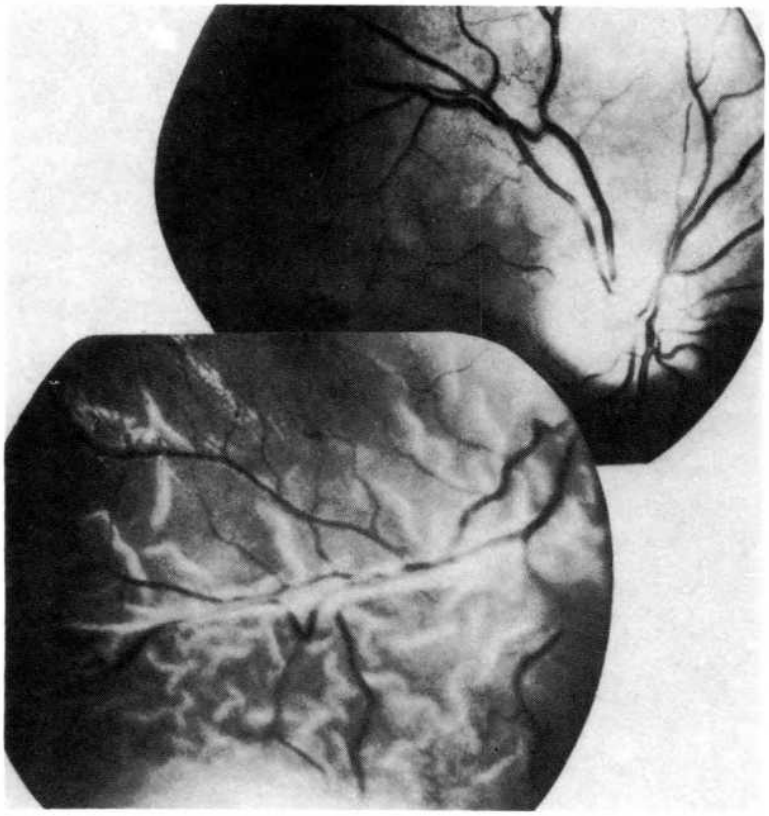

Fig. 1 *Case 1. Composite fundus photograph showing flat detached retina inferiorly and in the macula.*

thickness retinal tear, to settle. The inferior peripheral retina settled during the completion of the vitrectomy. Peripheral transscleral cryopexy was applied to the eye for 360°.

Postoperatively the retina remained attached (Fig. 2). At last examination seven months after surgery the best corrected visual acuity was 20/200.

CASE 2

A 2-year-old black boy had a red left eye that was diagnosed as viral conjunctivitis. On follow-up examination three weeks later the child was found to have a preretinal haemorrhage in the right eye and a possible retinal detachment in the left eye.

He was living in a foster home with his 3-year-old brother and no family history was available. Ocular examination of his brother was unremarkable.

Five weeks after his initial presentation the boy was admitted to hospital for an examination under anaesthesia. The right eye showed stellate cystoid changes in the macula and extensive retinoschisis in the inferior and temporal periphery, extending centrally with abrupt termination at the posterior pole. The left eye had a highly elevated bullous schisis cavity inferiorly overhanging and obscuring visualisation of the macula (Fig. 3). A second area of schisis was present in the superior temporal area.

The patient was again examined under anaesthesia six weeks later and underwent drainage of schisis fluid, vitrectomy to relieve traction on the inferior schisis cavity, and placement of an encircling silicone band in the left eye. Stellate cystoid changes were observed in the left macula after the schisis cavities were flattened.

He was readmitted for an examination under anaesthesia 10 months later. Examination of the left eye revealed a reaccumulation of fluid in the inferior and temporal schisis cavity, which again covered the macula. Three months later the child underwent surgery in the left eye, which involved drainage of fluid from both schisis cavities, and then scattered transscleral cryocoagulation was applied to the now flattened inferior and temporal schisis cavity. Twenty months after operation the retina remained attached (Fig. 4).

Nineteen months after the initial admission to hospital a vitreous haemorrhage (Fig. 5) and an inferior retinal detachment were discovered in the

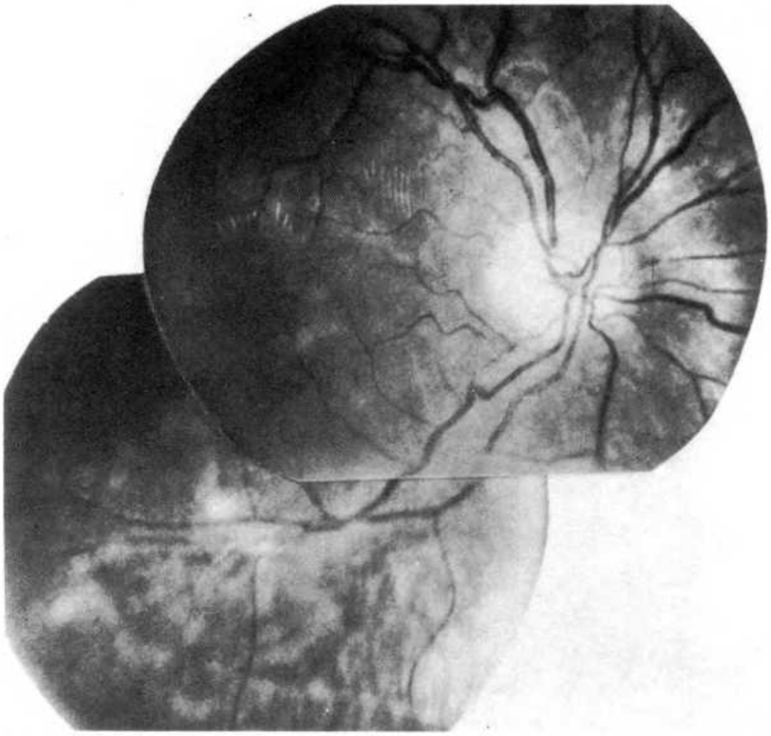

Fig. 2 *Case 1. Fundus photograph after vitrectomy and retinal detachment repair.*

right eye during routine examination. After a vitrectomy to remove blood from the vitreous cavity two large full-thickness retinal tears were observed. Subretinal fluid and fluid in the large schisis cavity was drained, and the two retinal tears were treated with cryopexy and an encircling silicone band, and a 5 mm radial silicone sponge was placed behind both retinal tears.

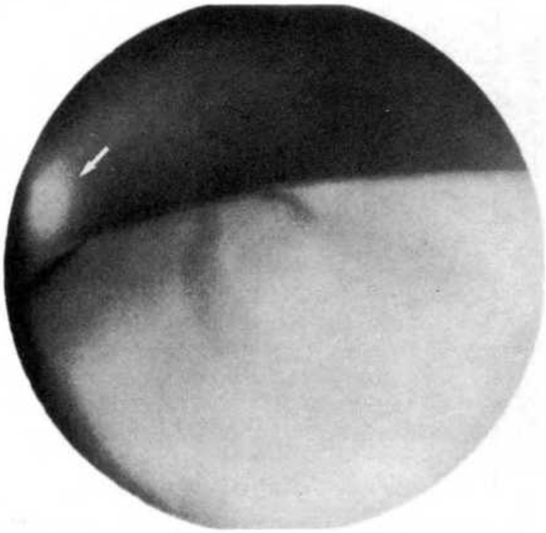

Fig. 3 *Case 2. Left eye fundus photograph showing huge schisis cavity covering the macular area. Arrow points to optic disc.*

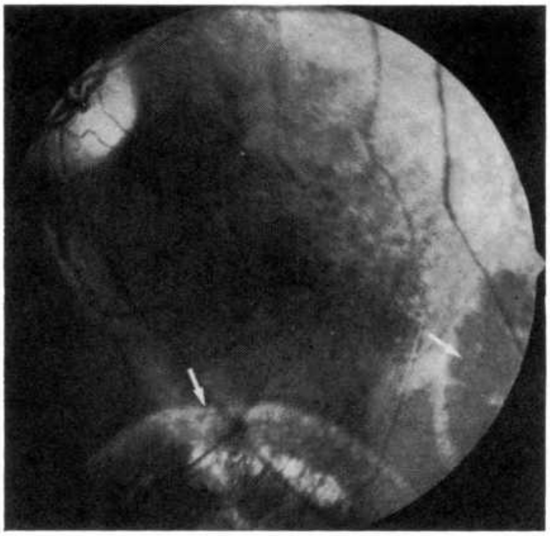

Fig. 4 *Case 2. Fundus photograph after vitrectomy, retinal detachment repair, and cryocoagulation. Note attached retina and typical schisis changes of the macula; arrows indicate cryocoagulation scar.*

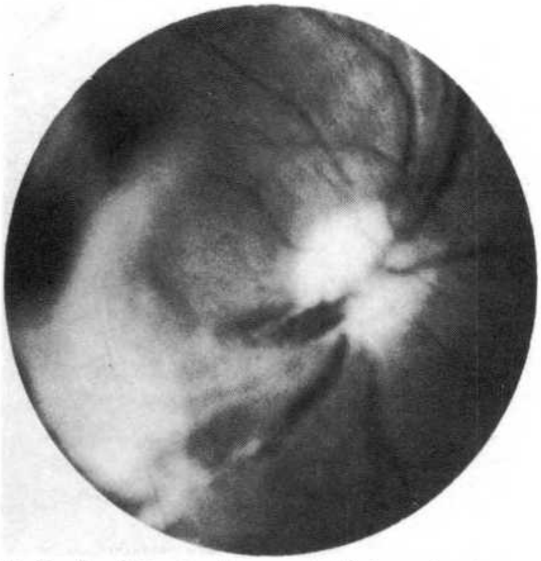

Fig. 5 *Case 2. Fundus photograph of right eye showing vitreous haemorrhage covering a detached inferior retina.*

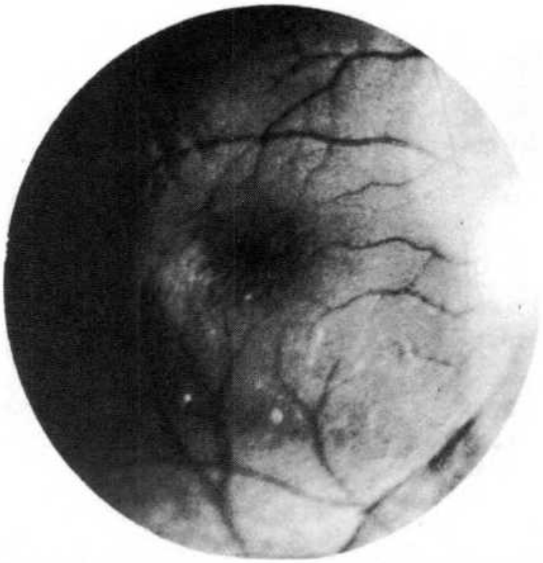

Fig. 6 *Case 2. Same eye as in Fig. 5 after vitrectomy, retinal detachment repair, and buckling procedure.*

Postoperatively a cataract developed in the right eye, which required a lensectomy a year later. At the time of the cataract surgery the retina and schisis cavities were noted to be flat (Fig. 6). Measurement of visual acuity was not possible because of the patient's youth.

Discussion

Congenital retinoschisis may be progressive or stationary or may spontaneously regress.[13] The clinical spectrum of ocular changes varies considerably among affected individuals. Deutman[20] states that macular retinoschisis occurs in all affected patients. Foveal retinoschisis in one report was present in 98% of involved individuals.[21] According to Deutman[20] in almost half the affected eyes macular lesions may represent the only sign of this disorder. The macular changes in older people may appear atrophic and pigmented.[22-24] Peripheral retinoschisis, characterized by intraretinal splitting involving the nerve fibre layer,[25] occurs in approximately 50% of eyes.[26] The inner layer is often immobile and elevated in a concave configuration. An absolute scotoma is present corresponding to the area of retinoschisis.[25]

Two severe vision-threatening complications of congenital retinoschisis are retinal detachment and vitreous haemorrhage.[12] Retinal detachments are caused by a combination of inner and outer layer holes in areas of retinoschisis, or retinal tears created by vitreous traction in abnormal retina.[13] Vitreous haemorrhage may result from vitreous traction on retinal vessels coursing through the elevated inner retinal layer of a schisis cavity.

A variety of vitreous pathology has been observed in eyes with congenital retinoschisis. All 15 patients in a series reported by Lisch[26] showed varying degrees of vitreous liquefaction. Vitreous strands were found in 50% of patients by Bec and associates.[27] Kraushar *et al.*[13] reported a series of 40 patients (77 eyes) with congenital retinoschisis. Retinal detachment developed in 22% of these affected eyes. Associated with retinal detachment were pathological vitreous changes, including vitreous membranes attached to and in some instances elevating the equatorial retina. Vitreous traction present in the posterior pole resulted in pseudopapilloedema (13% of eyes) and ectopic macula (6% of eyes). Vitreous haemorrhage occured in 40% of eyes. The investigators believed that in some instances vitreous haemorrhage was caused by traction on retinal blood vessels. Other less common signs of vitreous traction were tenting of the inner retinal layer (12%) or blood vessels (4%) and geographic areas of white without pressure (35%).

The retinas in both our patients and the inferior schisis cavity overhanging and obscuring visualisation of the macula were under vitreous traction. The retinas in both cases were successfully reattached following vitrectomy and scleral buckling. Vitrectomy in eyes with congenital retinoschisis is indicated when a significant tractional component is associated with either retinal detachment, elevation of a schisis cavity covering the macula, or vitreous haemorrhage originating from blood vessels located in the inner retinal layer of a schisis cavity. The tractional changes may result from proliferative vitreoretinopathy[28] complicating a retinal detachment or vitrous pathology inherent in congenital retinoschisis. Scleral buckling does not treat the vitreous pathology in these eyes, though it may relieve to some extent the tractional component of the retinal detachment. Vitrectomy is necessary to remove vitreous haemorrhage and to eliminate vitreous traction on the vessels and the retina.

Although vitrectomy prevents progression of vitreous tractional changes, it will not eliminate reaccumulation of fluid in the schisis cavity, as was the case in our second patient.

Drainage of subretinal fluid combined with cryocoagulation of the suspected retinal holes creates a permanent chorioretinal scar, thereby preventing reaccumulation of fluid in the schisis cavity.

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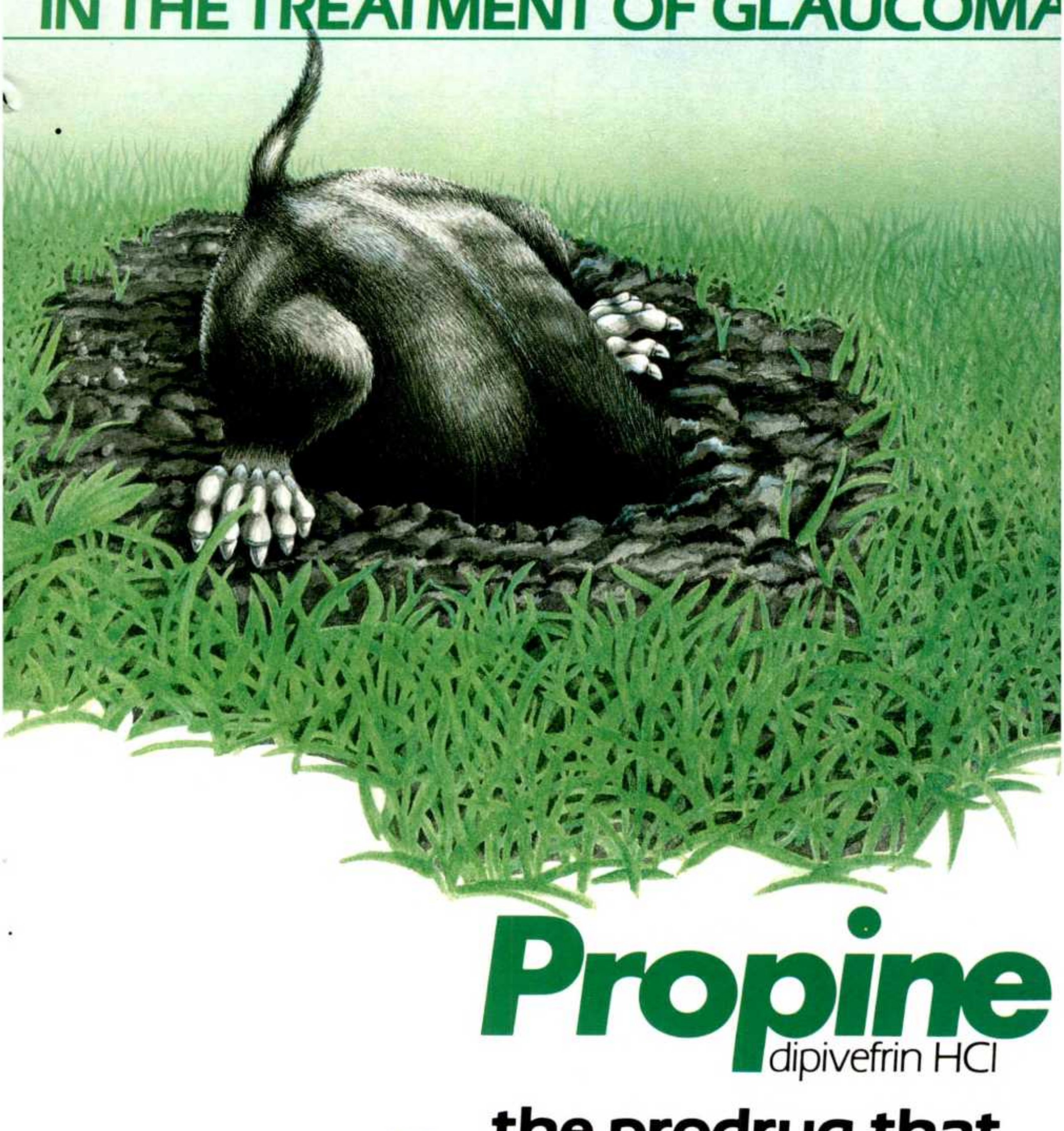

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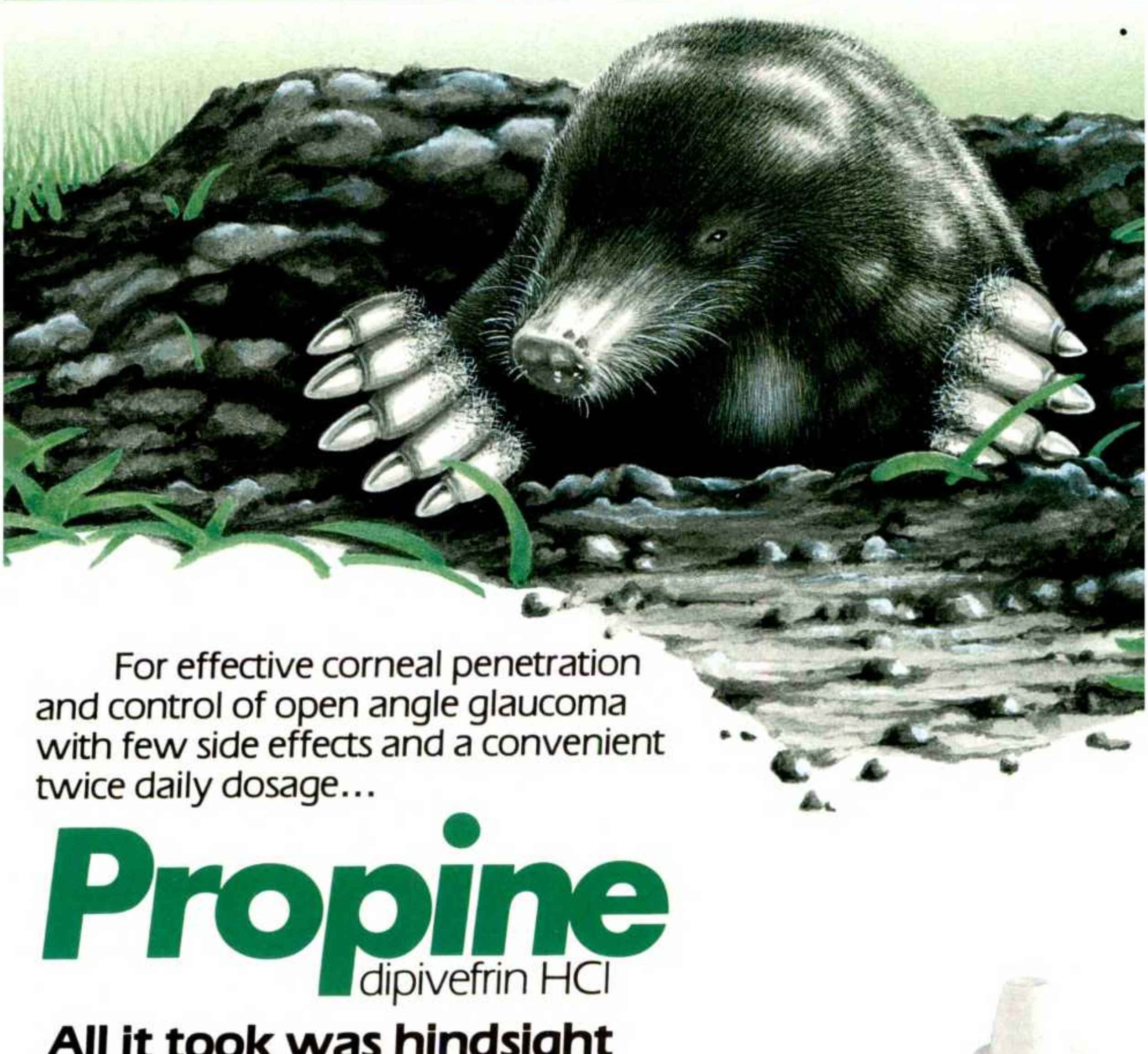

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British Journal of Ophthalmology, 1985, **69**, 487–490

Extracapsular lens extraction and posterior chamber intraocular lens insertion combined with trabeculectomy

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SUMMARY Trabeculectomy for primary glaucoma was successfully combined with extracapsular lens extraction and insertion of a Pearce tripod posterior chamber lens in seven eyes of five patients. The results were similar to those expected from each component of the operation when performed alone, and all eyes achieved visual acuity of 6/9 or better with control of intraocular pressure below 22 mmHg without supplementary medical treatment. The incidence of mild anterior uveitis (three out of seven eyes) and hyphaema (two out of seven eyes) was greater than usual with this type of cataract extraction but no more than expected after trabeculectomy. Mydriatic drops may be used to treat postoperative iritis without danger to the stability of this pattern of implant. In addition the anterior chamber cannot become shallow, as the rigid legs of this lens extend behind the iris beyond the periphery of the cornea and prevent forward movement of the implant even if there is excessively free drainage of aqueous after the operation.

In recent years authors from many countries have considered it an advantage to combine simultaneous trabeculectomy with lens extraction when cataract surgery becomes necessary in patients with glaucoma.[1-9] Earlier reports justified this combined operation only in cases where the intraocular pressure had been difficult to control medically, but recently the indications have widened to include cases where medical control has appeared satisfactory before cataract surgery. The risks and successes of the combined procedure are those of each component separately, and it reduces the chance of having to deal with the considerable problems in management of uncontrolled glaucoma in an aphakic eye.

The safety and optical advantages of intraocular lens implantation are now widely recognised, and, although Stiegler[10] has reported favourable results combining the insertion of a Kelman II anterior chamber lens when intracapsular extraction is combined with trabeculectomy, many surgeons would still hesitate to add lens implantation to the operation of cataract extraction combined with trabeculectomy. In 1979 Percival[11] succinctly summarised the practical problems, and de Heer[12] reviewed the limited reports on various lens types.

This paper describes the initial experience of satisfactory insertion of a single plane, rigid posterior chamber intraocular lens when trabeculectomy is combined with extracapsular lens extraction.

Material and methods

SURGICAL TECHNIQUE

The operation is essentially a combination of Watson's trabeculectomy[13] and extracapsular lens extraction with insertion of a sutureless Rayner-Pearce vaulted tripod posterior chamber lens in the capsular bag.[14] An adequate operating microscope with coaxial illumination is therefore essential to display the dissection of the lens capsule against the red reflex. Chloramphenicol eye drops are applied four times in the 24 hours before operation, and the pupil is fully dilated with 1% cyclopentolate and 10% phenylephrine immediately before surgery. This is supplemented with a subconjunctival injection of 0·25 ml of Mydricaine No. 2 (atropine, procaine, adrenaline), once the patient has been anaesthetised, so that full mydriasis is maintained during the

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intraocular dissection. It is wise to avoid dilating the pupil as part of the admission examination, because this preliminary exposure often renders the pupil refractory to subsequent dilatation at the time of operation. An outer sceral flap 4×4 mm is fashioned under a fornix based conjunctival flap, and the remainder of the corneoscleral incision for cataract extraction extends a further 6 mm to one side of the trabeculectomy site, so that the peripheral iridectomy at the trabeculectomy fistula will not coincide with the tip of the upper leg of the implant. After raising the superficial scleral flap and completing the corneoscleral ab-externo groove, the anterior chamber is entered in the depth of the groove with an irrigating cystitome through a puncture incision small enough to ensure a watertight seal. The D shaped anterior capsulotomy is then completed to fashion a deep inferior pocket before the inner corneoscleral block of the trabeculectomy is excised. Peripheral iridectomy is performed at the trabeculectomy site, and the trabeculectomy opening is then extended along the ab-externo groove incorporating the entry puncture used for capsulotomy. Thereafter the anterior capsule is removed, the pupil is swept behind the upper denuded part of the lens, and the lens is removed with an irrigating vectis. Any remaining cortex is aspirated manually with a coaxial aspiration-irrigation cannula, care being taken to preserve the posterior capsule. A sutureless Pearce tripod vaulted intraocular lens of suitable power is inserted into the inferior capsular pocket, and the upper leg (6·5 mm) is slipped behind the pupil into the iridociliary sulcus at the 12 o'clock meridian. The incision is closed with 10–0 nylon interrupted sutures at the corners of the trabeculectomy flap and along the corneoscleral wound.

Postoperative treatment consists of chloramphenicol and betamethasone drops applied four times daily with a mydriatic regimen of once daily intensive dilatation of the pupil with cyclopentolate and phenylephrine drops combined with a regular prescription for cyclopentolate or atropine as necessary. The eye is bandaged for the first two days, and the patient is discharged between the 3rd and 6th day, depending on home circumstances.

PATIENTS

The operation was performed on seven eyes of five consecutive patients who had primary glaucoma requiring treatment and who were otherwise suitable for extracapsular lens extraction with intraocular lens implantation. There were four female and one male patient, whose ages ranged between 68 and 81 years (mean 73 years). Four had primary open angle glaucoma and one had chronic angle closure glaucoma with 30% peripheral anterior synechiae. Visual field analysis with a Tubingen perimeter had suggested arcuate visual field defects diagnostic of glaucoma in four patients when first examined and before the development of dense cataract. The fifth patient had advanced cataract when first examined and accurate visual field testing was not possible. For each eye the maximum intraocular pressure without medical therapy ranged from 24 to 36 mmHg (average 28 mmHg). No eye had had previous surgery.

Results

Patients have been followed up for two to 36 months (mean 18 months). In all eyes vision was restored to 6/9 or better, and the intraocular pressure was reduced to below 22 mmHg without supplementary medical therapy. Fig. 1 shows the maximum untreated preoperative intraocular pressure and the postoperative levels. The effect of this combined operation, as demonstrated by the straight line relating the reduction in intraocular pressure to the initial maximum untreated pressure, is similar to that found when trabeculectomy alone was carried out in

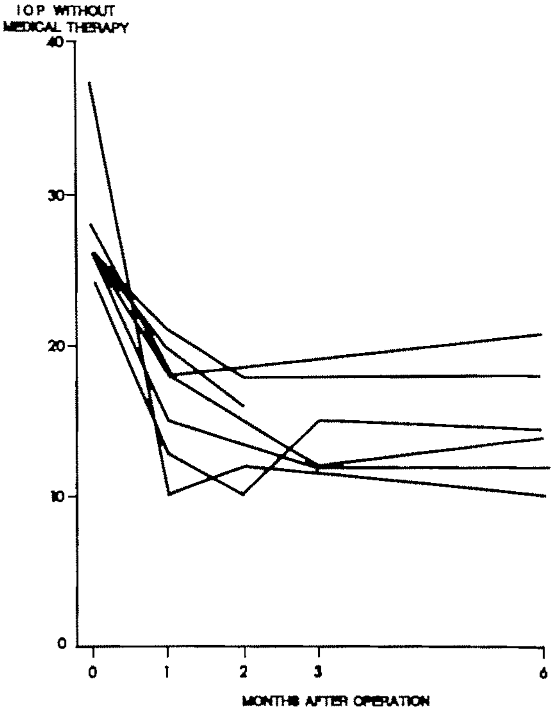

Fig 1 *Reduction of intraocular pressure from untreated preoperative levels after trabeculectomy combined with extracapsular lens extraction and insertion of a Pearce tripod posterior chamber lens No medication was required to reduce the postoperative intraocular pressure.*

phakic eyes with primary open angle glaucoma (Fig. 2).

The postoperative course was as expected with hyphaema (two cases) and iritis (three cases) occurring with the frequency and severity observed after trabeculectomy alone. The hyphaemas resolved within two days in both cases, and in all cases the anterior chamber inflammation settled quickly so that the postoperative eye drops could be discontinued within six weeks. It was, however, impossible to prevent minor posterior synechiae between iris and capsule remnants in four eyes. The field of vision showed considerable improvement in the five eyes of the four patients who were tested preoperatively, and after operation only minor relative arcuate defects remained. In the other patient the postoperative field tests revealed minor arcuate defects in one eye and no abnormality in the other.

No patient has shown subsequent visual field deterioration or loss of control of intraocular pressure. None of the patients had optic nerve cupping of greater than 0·6 vertical cup to disc ratio when last examined, which confirms the relatively early stage of optic nerve disturbance in all the cases described.

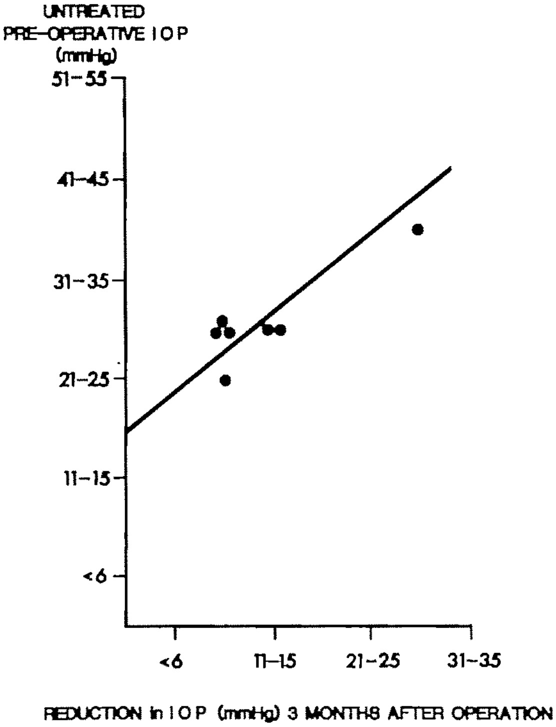

Fig 2 *Straight line relationship between untreated preoperative intraocular pressure and the reduction in pressure achieved by a first trabeculectomy in primary open angle glaucoma, redrawn from Jay and Murray* [11] *The results of the combined operations (black circles) show a similar effect on intraocular pressure.*

Discussion

Although the number of cases is small the results suggest that the effect of this type of combined operation is to achieve the visual benefits of cataract extraction with intraocular lens implantation as well as the intraocular pressure control expected after trabeculectomy. Combining the two procedures does not seem to introduce new complications. The visual results are similar to those in the author's unpublished Pearce posterior chamber lens series, and Fig. 2 confirms that the reduction of intraocular pressure is identical to that following a first trabeculectomy for

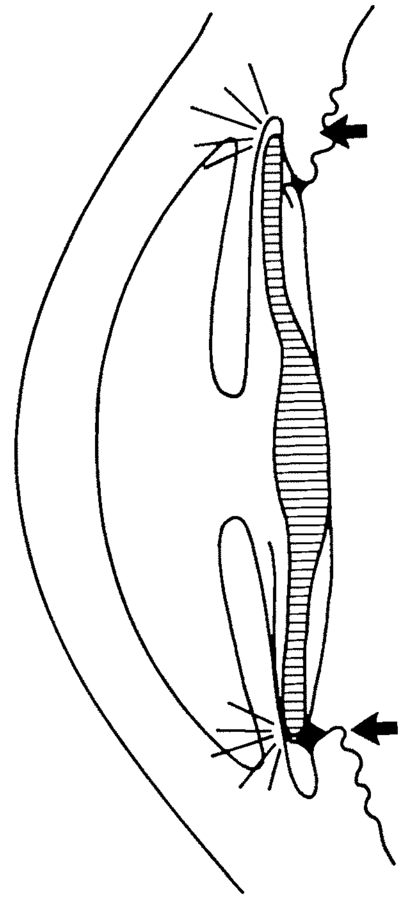

Fig. 3 *Cross-sectional diagram of a Pearce tripod posterior chamber lens in place. The position of the rigid legs of this lens (arrowed) will prevent forward displacement and shallowing of the anterior chamber even in the event of excessive drainage of aqueous*

primary open angle glaucoma where the intraocular pressure is lowered to the physiological range irrespective of the preoperative pressure.[15] The observed visual field improvement was probably a result of improved retinal illumination following removal of the cataractous lens.

After trabeculectomy the risk of shallow or flat anterior chamber in the presence of an intraocular lens might be hazardous, but the Pearce tripod lens is a single plane lens with no component in front of the pupil, and its rigid legs act as radial struts to stop the implant moving forwards even with excessive drainage of aqueous. This implant will therefore prevent the anterior chamber becoming shallow (Fig. 3), a feature which is also useful when intraocular lens insertion is combined with penetrating keratoplasty. It is not known whether posterior chamber lenses with flexible loops will prove stiff enough to prevent loss of the anterior chamber in this manner, and for various reasons iris plane lenses and rigid angle supported lenses are best avoided in glaucomatous eyes.[16]

Many glaucoma patients may have used miotic drops for years before surgery, and adequate dilatation of the pupil for extracapsular cataract may be impossible. In these cases the pupil may be enlarged surgically during the operation by a radial iridotomy from iris root to pupil, and after insertion of the implant the pupil is restored by suturing the iris.

It seems that, where a surgeon is experienced in this technique of cataract surgery, it is now possible to offer patients the benefit of combining intraocular lens implantation with glaucoma surgery. It is, however, still necessary to select patients with caution, as experience is limited to seven eyes which were eventually found to have good residual optic nerve function.

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Assessment of bleeding in eye surgery

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SUMMARY A new method for assessing microhaemorrhage in eye surgery was used in 16 patients for cataract extraction. It was shown that bleeding was greatest in the first five minutes and that it correlated with the surgeon's clinical estimate of blood loss. The method was used to assess the effect of two different general anaesthetic induction regimens on intraoperative bleeding.

In many types of eye surgery a small amount of bleeding makes a large difference to the operative field and ease of surgery. Etomidate is a relatively new intravenous general anaesthetic induction agent which has been shown to cause a fall in intraocular pressure.[1] It was noted that following the use of etomidate the eye appeared less injected, and surgeons spontaneously commented that the operating field was better than usual. A technique for measuring the bleeding in cataract surgery was therefore developed to compare the difference between the operative fields during cataract surgery after induction of anaesthesia with etomidate or thiopentone.

Patients and methods

Sixteen patients were studied who were undergoing elective intracapsular cataract extraction under general anaesthesia at the Oxford Eye Hospital. Their ages ranged from 58 to 92, and their general medical fitness was based on the American Society of Anaesthesiologists' classification. Twelve were ASA 2, 3 were ASA 1, and 1 was ASA 3. The ASA gradings are: class 1, a normal healthy patient; class 2, a patient with mild systemic disease; class 3, a patient with severe systemic disease which is not incapacitating; class 4, a patient with an incapacitating systemic disease which is a constant threat to life, class 5, a moribund patient not expected to survive longer than 24 hours with or without operation.

Two standard techniques of anaesthesia were used differing only in the choice of induction agent. Etomidate or thiopentone was chosen on a random basis, and only the anaesthetists knew which one was used. Blood pressure was maintained within ±20% of preinduction values, and the end-tidal carbon dioxide was maintained at 4% by intermittent positive pressure ventilation in all except four cases, when the monitor malfunctioned.

A standard ab externo technique of cataract extraction was used, with conjunctival flap, limbal groove, two preplaced and three postplaced 8/0 virgin silk interrupted sutures, razor entry, and completion of the section with scissors. Chymotrypsin was used routinely, and the lens was cryoextracted.

The time from the start of induction to the first conjunctival incision was noted, and cellulose swabs were used frequently to absorb blood in the operative field. These were collected in batches covering each five-minute interval for the first 15 minutes, and the remaining swabs used were batched at the end of surgery. The surgeon was asked for his clinical assessment of bleeding on a scale of 0–10 (0 being equivalent to zero bleeding) at the time of each collection. Care was taken by the surgeons to collect all blood on the swabs.

Collected swabs were immediately placed into Drabkin's solution and the blood loss estimated in the laboratory at a later date. 5 ml of the patient's venous blood was taken during the first five-minute swab collection period for haemoglobin estimation.

ASSESSMENT OF BLOOD LOSS

The swabs were collected directly into 20 ml of Drabkin's solution in a universal tube. At the end of the operation the number of swabs in each tube was counted and extra prewetted swabs added as necessary, so that there was the same number in each tube. This was done in order to minimise effects due to absorption of haemoglobin on to the swabs.

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Haemoglobin was measured by conversion to cyanmethaemoglobin with Drabkin's reagent (Diagnostic Reagents Ltd, Thame). The absorption of the cyanmethaemoglobin at 540 nm was then compared with that of a standard solution. The precision of the method was 5% and the sensitivity was 1 µl. The haemoglobin content of the edetic acid (EDTA) sample of the patient's blood was measured in triplicate after dilution of 10 µl in 4 ml of Drabkin's solution. Calculation of the volume of blood taken up into swabs was as follows:

$$V = 100 \times S \times 1000/5 \times B \ \mu l,$$

where V is volume of blood, S is concentration of haemoglobin eluted into Drabkin's reagent, and B is the patient's peroperative haemoglobin concentration.

Results

Most of the blood losses occurred during the first five-minute collection period, although there was a marked variation in values (Fig. 1), which is in keeping with clinical experience.

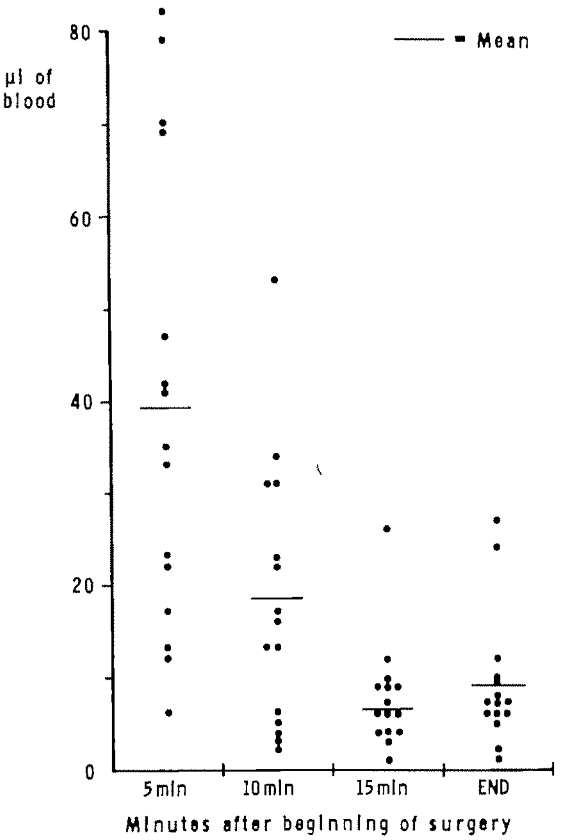

Fig 1 *Mean blood losses and the scatter of results during each collection period*

The surgeon's clinical estimates of blood loss correlated well with the measured blood losses. The Spearman correlation coefficient was 0·711 ($p<0{\cdot}01$). For this calculation the blood loss values were converted to a non-parametric scale.

There was no statistically significant relationship found between blood loss and the anaesthetic technique used. The mean interval from induction to operation was 14·6 min (range 9–23).

Discussion

It is generally held that the degree of congestion of the operative field and hence the likelihood of haemorrhage during surgery is influenced by anaesthetic agents and technique. Even small extravasations can obscure surgical detail during microsurgery, and therefore it was of interest to see whether such blood loss could be measured accurately over the operative course, and also to determine whether two different induction agents might have a different effect on blood loss during cataract surgery when a standard anaesthetic technique was used. Only one other study of this kind was found.[2]

Etomidate was chosen as a suitable induction agent for general anaesthesia because of its good cardiovascular stability, rapid metabolism, and ability to lower intraocular pressure.[1] The subjective observation by ophthalmic surgeons that its use was followed by less bleeding than with a standard thiopentone induction was not substantiated in the present study.

The method used here for measuring blood loss is accurate, sensitive (sensitivity 1 µl compared with 5 µl in Clements's study[2]), and correlates well with clinical impression. Immediate immersion of swabs into Drabkin's solution allows a more complete elution of blood before it dries. The good correlation between measured blood loss and the surgeon's estimate suggests that the surgeon can make a reasonable assessment of blood loss during surgery.

In summary, it was not possible to demonstrate a difference in effect of two induction agents on microhaemorrhage into the operative field during cataract surgery. However, a technique has been described for the simple measurement of such haemorrhage which could be applied to the assessment of bleeding during other microsurgical procedures.

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Medical conditions underlying recurrence of retinal vein occlusion

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SUMMARY Seventeen patients with recurrent retinal vein occlusion were investigated for underlying medical conditions and compared with 61 patients with single retinal vein occlusion (26 with central, 35 with branch vein occlusion). The two study groups were comparable for age, sex, and weight. Patients with recurrence had a significantly increased prevalence rate of hypertension (88% versus 48%: $p<0.01$), with a trend to increased hyperlipidaemia (47% versus 33%) compared with patients with a single episode. A significantly raised mean systolic ($p<0.05$) but not diastolic blood pressure was found in patients with recurrence. Other cardiovascular risk factors in patients with recurrence were also found and included lower mean levels of high density lipoprotein (HDL)-cholesterol ($p<0.02$) and the HDL_2 subfraction ($p<0.001$), and a significantly increased proportion of patients with regular alcohol intake ($p<0.01$). We conclude that hypertension and hyperlipidaemia with an increase in other cardiovascular risk factors are commonly found in patients with recurrent retinal vein occlusion and may therefore be important aetiological factors. The possible benefits of treatment of these underlying conditions to prevent recurrence need to be assessed in well designed prospective studies.

Retinal vein occlusion is a common cause of visual loss in the United Kingdom. Its exact aetiology is unclear and therefore medical treatment is unsatisfactory. Management of it is aimed at identifying and treating the complications of retinal vein occlusion, and underlying medical conditions, for example, hypertension, hyperlipidaemia, diabetes mellitus, enhanced platelet activity, or hyperviscosity syndromes.[1-5]

However, reports have suggested that 15% of patients who have had a single retinal vein occlusion will go on to have another, commonly in the previously non-affected eye, with a consequent disastrous visual outcome.[6] Patients with recurrent retinal vein occlusion have not been studied separately from those with single retinal vein occlusion, and so no data are available on why patients have a recurrence or which ones will do so.

We have therefore performed a study to identify the prevalence of medical conditions associated with recurrent retinal vein occlusion as compared with cases of single occlusion. Special emphasis has been paid to cardiovascular risk factors, including hypertension, hyperlipidaemia, and lipoprotein levels. These include the positively associated low density lipoprotein (LDL) and the negatively associated high density lipoprotein (HDL)-cholesterol and one of its subfractions HDL_2.[7]

Patients and methods

Sixty-one patients with single retinal vein occlusion (26 with central and 35 with branch retinal vein occlusion) and 17 patients with recurrent retinal vein occlusion were investigated serially with no prior selection at Birmingham and Midland Eye Hospital. The diagnosis of retinal vein occlusion, apart from suggestive clinical history and funduscopy, was confirmed by fluorescein angiography. Further clinical examination included a search for the presence of large vessel disease and a history of current drug therapy. After full clinical examination the following investigations were performed: full haematological profile, liver function tests, fasting lipid profile, and blood sugar.

Blood pressure was recorded after five minutes' rest in the sitting and supine position on an Accuson

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sphygmomanometer and the mean recorded. Diastolic pressure was recorded at the fifth Korotkoff phase.

Hypertension was defined as three consecutive blood pressure recordings of systolic greater than 160 mmHg and diastolic greater than 95 mmHg or when a patient was already established on antihypertensive drug therapy. Hyperlipidaemia was defined as a fasting serum cholesterol level greater than 7·1 mmol/l or serum triglyceride level greater than 2·1 mmol/l.

Serum cholesterol and triglyceride were measured by standard semiautomated techniques. HDL-cholesterol was measured in the supernatant fraction following precipitation of very low density lipoprotein (VLDL) and LDL by heparin (250 units/50 μl) and 1 M manganese chloride (50 μl) (coefficient of variation 2%).[8] Further precipitation of the supernatant containing HDL with 100 μl low molecular weight dextran sulphate (14·3 g/l) as reported by Ferns *et al.* allowed measurement of the HDL$_3$ subfraction.[9] The HDL$_2$ cholesterol level was calculated by subtraction of HDL$_3$ level from the total HDL cholesterol level. The results of HDL$_2$-cholesterol measured by precipitation correlated well with results of preparative ultracentrifugation (r=+0·978, p<0·001).[10] VLDL-cholesterol was measured after precipitation by sodium dodecyl sulphate (100 g/l in 0·15 M sodium chloride; 75 μl). LDL-cholesterol was obtained by subtracting the sum of HDL and VLDL cholesterol from the total serum cholesterol.

Table 1 *Clinical details of patients studied with a single episode and recurrent vein occlusion*

Group		*Form of retinal vein occlusion*	*Mean age (yr)*	*Mean weight (kg)*
Single retinal vein occlusion (n=61)	27M 34F	BRVO (35) CRVO (26)	61·0 ±13·6	70·1 ±12·4
Recurrent retinal vein occlusion (n=17)	9M 8F	Bilateral BRVO (6) Bilateral CRVO (6) Central and BRVO (5)	65·94 ± 9·63	72·42 ±15·6

BRVO and CRVO=Branch and central retinal vein occlusion respectively

Statistics were by unpaired *t* test and the χ^2 test with Yates's correction factor.

Results

The clinical details of the patients studied are shown in Table 1. The two groups were well matched for clinical details apart from the smaller number of patients in the recurrence group. This difference was expected owing to the low incidence of recurrence in those patients with single retinal vein occlusion.

Table 2 presents the prevalence of associated diseases in the two groups. The prevalence rates of associated medical conditions in the group of patients with single retinal vein occlusion used for comparison in this study were similar to those of larger series.[2,3]

There was a significantly increased prevalence rate of hypertension (p<0·01) and a trend to an increase in the prevalence of hyperlipidaemia in those patients with recurrence compared with those with a single retinal venous event. The prevalence rates of hypercholesterolaemia and hypertriglyceridaemia showed an increase in the recurrent group, though this did not reach statistical significance. No significant differences were also observed (Table 3) between mean total serum cholesterol triglyceride and LDL-cholesterol levels, but mean total HDL-cholesterol levels (p<0·02) were significantly reduced in the recurrent group. This difference was due to a reduction in mean HDL$_2$-cholesterol levels (p<0·001) and not in HDL$_3$ levels.

There was no difference between the groups with

Table 2 *Prevalence rates of associated conditions in patients with single and recurrent retinal vein occlusion*

	Hypertension	*Hyperlipidaemia*	*Hypercholesterolaemia*	*Hypertriglyceridaemia*
Recurrent retinal vein occlusion (n=17)	88% (15)	47% (8)	35% (6)	24% (4)
Significance	p<0·01	NS	NS	NS
Single retinal vein occlusion (n=61)	48% (29)	33% (20)	28% (17)	15% (9)

Statistics by the χ^2 test NS=not significant

Table 3 *Serum lipid and lipoprotein levels in patients with single and recurrent retinal vein occlusion*

	Mean serum cholesterol (MM)	*Mean serum triglyceride (MM)*	*Mean HDL cholesterol (MM)*	*Mean HDL_2 cholesterol (MM)*	*Mean HDL_3 cholesterol (MM)*	*Mean LDL cholesterol (MM)*
Recurrent retinal vein occlusion	6·36	1·69	1·24*	0·30†	0·93	3·35
(n=17)	±1·6	±0·74	±0·3	±0·11	±0·31	±1·12
Single retinal vein occlusion	6·3	1·37	1·46	0·52	0·95	3·17
(n=61)	±1·4	±0·7	±0·3	±0·24	±0·25	±1·26

Values are mean±SD *p<0·02. †p<0·001
HDL=high-density lipoprotein LDL=low-density lipoprotein

regard to the number of current cigarette smokers (23·5 versus 22·9%). In contrast, there was a significantly greater proportion of patients with a current regular alcohol intake (>7 g of alcohol/day) in the recurrent group than in the group with single retinal vein occlusion (47% versus 13%: p<0·01).

Further analysis with regard to blood pressure in the two groups (Table 4) revealed a significant increase in mean systolic blood pressure (p<0·01) in the recurrent group, but the minor increase in diastolic blood pressure did not reach statistical significance. Table 5 analyses those patients with hypertension in the two groups. Of 15 patients with hypertension in the recurrent group seven were newly diagnosed and eight were on prior antihypertensive medication. However, to emphasise the possible importance of good blood pressure control only three patients on prior medication had normal blood pressure recordings.

Discussion

The striking result in this study is the finding of such a high prevalence rate of hypertension (87%) in those patients with recurrent retinal vein occlusion. This finding, in conjunction with the raised mean levels of blood pressure and the high number of patients with poor control of hypertension, lends further strong support to the view that hypertension is a major aetiological factor. This is supported by the recent observation of poorly controlled hypertension in five of eight patients who developed recurrence of retinal vein occlusion during a five- to 10-year follow-up period.[11] These observations may also have implications with regard to the life expectancy of patients with retinal vein occlusion, as in a 10-year prospective study of 226 patients the proportion with a vascular cause of death (cardiac or cerebral) was about double that expected from mortality statistics compiled for England and Wales.[4] In view of the evidence that drug treatment of hypertension may reduce some hypertensive complications, particularly cerebrovascular episodes,[12] it seems likely that good control of hypertension should reduce the mortality of patients with retinal vein occlusion from vascular causes and possibly recurrence of retinal vein occlusion. That retinal vein occlusion and cerebrovascular disease have a common aetiology in hypertension is therefore clear, but the situation differs in patients of different ethnic groups. For example, it has recently been noted that retinal vein occlusion, particularly the central form, is rarely seen

Table 4 *Mean blood pressure levels in the patients with single and recurrent retinal vein occlusion*

	Mean systolic blood pressure (mmHg)	*Mean diastolic blood pressure (mmHg)*
Recurrent retinal vein	175*	92·1
occlusion (n=17)	± 30·2	±10·0
Single retinal vein	156·6	88·6
occlusion (n=61)	± 26·4	±10·2

Figures are mean±SD. *p<0·05 by unpaired *t* test

Table 5 *Hypertension in the two groups of patients with retinal vein occlusion*

Hypertensive group	*Percentage and number of patients*		
	Newly diagnosed	*On prior antihypertensive medication*	*On prior antihypertensive medication but still hypertensive*
Recurrent retinal vein occlusion (n=15)	47% (7)	53% (8)	63% (5)
Single retinal vein occlusion (n=29)	38% (11)	62% (18)	44% (8)

in blacks in two major ophthalmological centres serving large West Indian populations,[13] but it is this group who have been reported to have the highest prevalence of hypertension associated with a high incidence of cerebrovascular disease.[14] Furthermore, hypertension is often severer in blacks than in the white community, in whom retinal vein occlusion is evidently more common.[14]

The exact mechanism of retinal venous damage by hypertension is unclear but possibilities include increased inflammatory activity, which has been demonstrated in hypertensive patients with retinal vein occlusion,[15 16] or indirect vascular damage to the retinal vein. This in turn may lead to vascular degeneration, with deposition of platelet aggregates.

Other cardiovascular risk factors for recurrence found in this study include an increased prevalence of hyperlipidaemia and reduced levels of HDL-cholesterol and its subfraction HDL_2. These findings might just express the presence of generalised vascular disease per se, but this is doubtful, as the prevalence of hyperlipidaemia appears to be significantly greater in patients with retinal vein occlusion than in control subjects with the same prevalence of overt macrovascular disease.[3] Furthermore a significant postive relationship has been demonstrated between increasing serum cholesterol levels and the severity of retinal venous lesion on fluorescein angiograms.[3] It would therefore appear that hyperlipidaemia may also be aetiological in single and recurrent retinal vein occlusion and that, in patients with a single retinal venous event, hyperlipidaemia and a low serum HDL-cholesterol might be more at risk of recurrence.

It is also of interest that there was a significant increase in the number of patients with a regular alcohol intake in the recurrence group. This may be a factor in the aetiology of the increased hyperlipidaemia and hypertension observed in this group. Smoking, another important cardiovascular risk factor, was not different in the two study groups.

Although no conclusions on the benefit of treating associated conditions to prevent recurrence can be made, this study does suggest the possibility that treatment of hypertension and hyperlipidaemia in these patients might be of value to prevent recurrence. This hypothesis has indeed recently been tested but in a non-controlled retrospective study of 22 hypertensive patients with retinal vein occlusion. The results were disappointing in that recurrence was not prevented, but this may well be due to the poor hypotensive control achieved by drug treatment and the failure to include treatment for hyperlipidaemia in this study.[17]

We conclude that hypertension and hyperlipidaemia, with an increase in other cardiovascular risk factors, are found in patients with recurrent retinal vein occlusion. These may therefore be important aetiological factors, but the exact mechanisms and the possible benefits of treatment need to be assessed in well designed prospective studies.

We are grateful to all the staff of the Medical Ophthalmology Clinic and Mrs B Singh for secretarial help.

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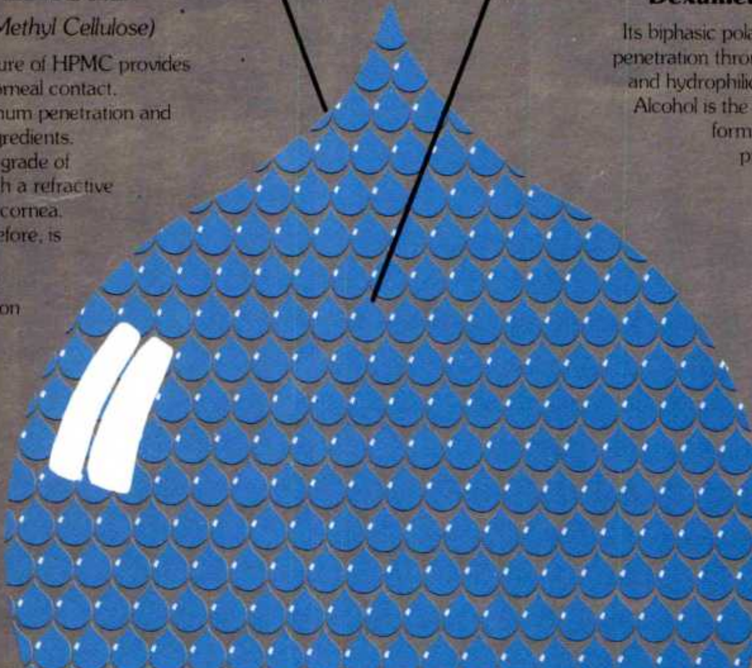

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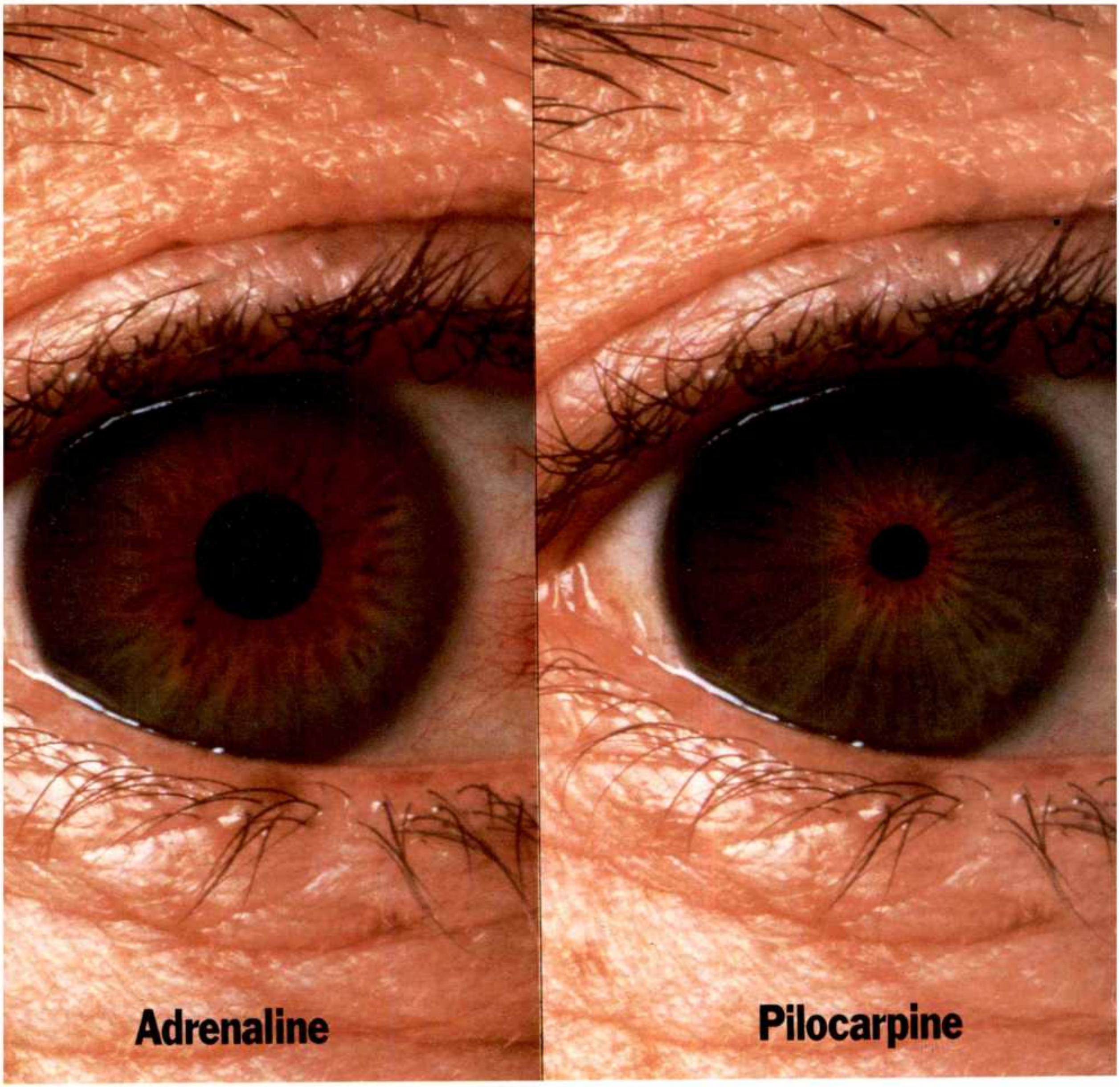

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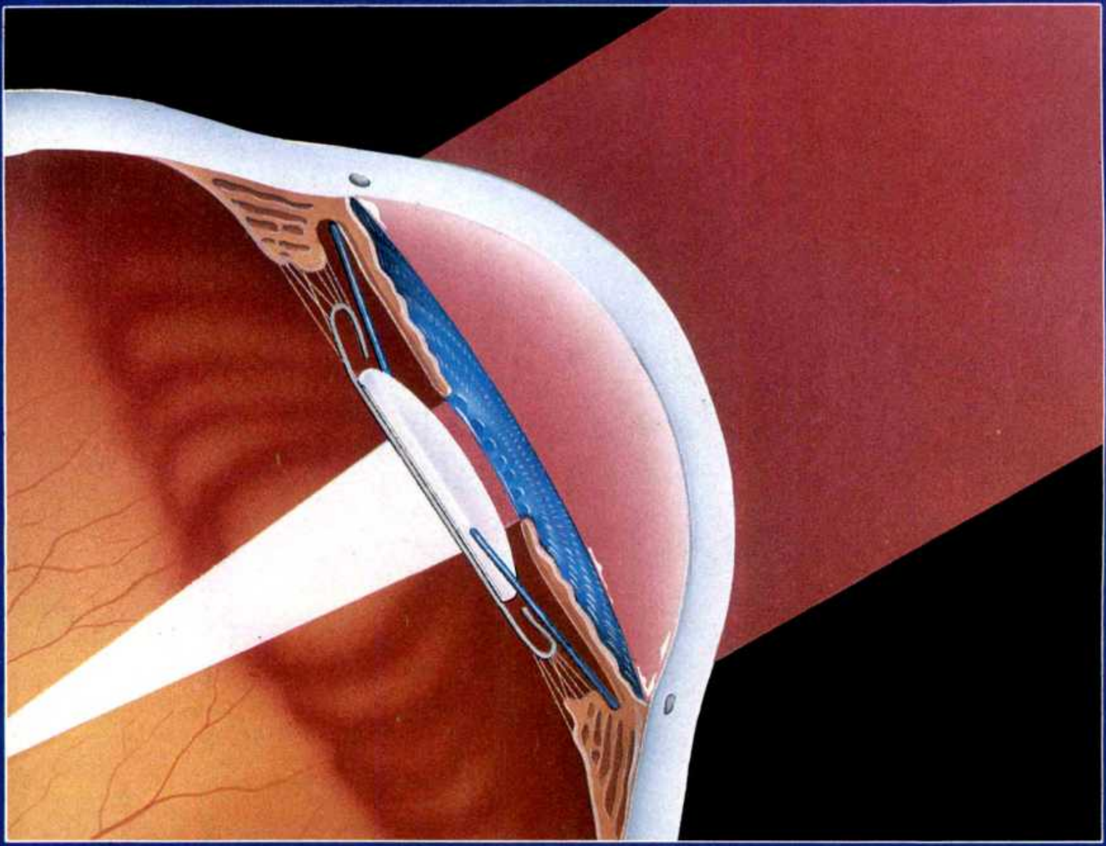

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α_1 Antitrypsin serum levels and phenotypes in patients with retinal vasculitis

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SUMMARY α_1 antitrypsin is an important immunoregulatory protein, the serum level of which is genetically determined. Deficient phenotypes of this ubiquitous protease inhibitor are associated with a variety of inflammatory diseases including anterior uveitis. In order to investigate the role of this protease inhibitor in the pathogenesis of retinal vasculitis (RV) 25 patients were investigated. Diseases associated with RV included Behçet's syndrome (8), SLE (2), and sarcoidosis (1). Deficient phenotypes of α_1 antitrypsin were not associated with RV. However, the serum α_1 antitrypsin level was significantly increased in patients with active RV and paralleled disease activity in patients studied prospectively.

Immunogenetic factors, especially HLA antigens, have been shown to be associated with a variety of inflammatory eye diseases, particularly those affecting the uvea. There is increasing evidence that other immunogenetic markers such as deficient phenotypes of the α_1 protease inhibitor Pi (α_1 antitrypsin) are important markers of ocular disease susceptibility. Severe α_1 AT deficiency (PiZZ) was originally reported by Laurell and Eriksson[1] to be associated with emphysema. Subsequent investigations suggest that even mild degrees of Pi deficiency are associated with many inflammatory and immunologically mediated conditions. Among such disorders are chronic liver disease, rheumatoid arthritis, juvenile chronic arthritis, systemic lupus erythematosus, fibrosing alveolitis, ankylosing spondylitis, and anterior uveitis.[2,3]

The serum concentration of Pi is genetically determined.[1] The genes regulating Pi are linked to that governing the Gm marker on IgG,[3] are not in the HLA region, and have recently been shown to be coded for by codominant alleles on chromosomes 14.[4] The serum level of Pi does not accurately reflect the underlying Pi phenotype, and these proteins act as acute phase reactants, their level being increased by a number of drugs as well as infection and other inflammatory disorders.[5,6] Thus people with mildly deficient phenotypes PiMS or PiMZ may have serum levels in the normal range, and electrophoretic techniques are required to detect these phenotypes.[6]

Recent studies in our department have indicated that retinal vasculitis (RV) is associated with the HLA-DR4 antigen.[7] In order to examine further the role of immunogenetic factors in RV a group of 25 patients with well characterised RV were investigated.

Material and methods

Patient selection. Twenty-five patients referred to the Uveitis Research Clinic at Sydney Eye Hospital or the Department of Immunology, St Vincent's Hospital, were investigated. Retinal vasculitis is defined as inflammation confined predominantly to the retinal vessels. The criteria for the diagnosis of RV is based on the presence of typical ocular signs as outlined by Ffytche[8] and Sanders[9] and supported by fluorescein angiographic evidence of RV with focal areas of vascular leakage, local dilatation, and narrowing or occlusion of veins with associated retinal oedema.[8,10] All patients were seen independently by at least two ophthalmologists and a physician. Retinal fluorescein angiograms were performed on all patients and were reported indepen-

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dently to be consistent with the diagnosis of RV. Control subjects for serum α_1 antitrypsin determination consisted of 161 normal persons. A population of 339 blood donors had previously been studied to determine the normal distribution of α_1 antitrypsin phenotypes (Table 2).

Aetiological investigations. All patients had a chest *x*-ray done, full blood count, erythrocyte sedimentation rate, and biochemical screen including liver function tests, calcium and angiotensin converting enzyme, serological tests for syphilis, toxoplasma, and viruses (cytomegalovirus, herpes simplex, and hepatitis B), for autoantibodies, and a urine analysis.

α_1 *Antitrypsin serum determination.* Serum levels of α_1 antitrypsin levels were determined by standard radial immunodiffusion plates (Hyland Diagnostics).

α_1 *Antitrypsin phenotyping.* This was carried out by the technique of flat bed isoelectric focusing on polyacrylamide gels at pH 3·3–5·0.[11] Where necessary, resolution was enhanced by immunofixation techniques.[12 13]

Results

RETINAL VASCULITIS PATIENTS

The disease associations in the 25 patients with RV are summarised in Table 1, while Table 2 details the serum α_1 antitrypsin phenotypes of individual patients with RV. The mean age of onset was 35 years SD 11·1, range 17–54. There were 13 females in the study population, with a mean age of 38 years, SD 11, range 21–54, and 12 males with a mean age of onset of 31 years, SD 10, range 17–44.

AETIOLOGY AND DISEASE ASSOCIATIONS

Relevant associated diseases were present in 11 of the 25 patients with RV (Tables 1 and 2). Behçet's syndrome was the most common disease association, being present in eight patients (five females). It was diagnosed clinically by the presence of oral and genital ulcers together with eye disease. Two patients had SLE diagnosed on the basis of ARA criteria[14] and the presence of significantly raised titres of DNA antibodies. The clinical features of this group of patients have been previously reported.[7]

α_1 ANTITRYPSIN SERUM LEVELS AND PHENOTYPES

The mean serum α_1 antitrypsin level in RV patients was 2·5 g/l (SD 0·5), and this was significantly higher than in controls (mean 1·6 g/l, SD 0·5); $p<0·05$, Student's *t* test (Table 1). The serum α_1 antitrypsin level decreased with the introduction of steroid therapy and remained at normal levels in patients whose disease was in remission. In three persons who experienced a relapse in their RV the clinical deterioration was accompanied by an increase in serum α_1 antitrypsin levels.

Table 1 α_1 *Antitrypsin serum levels and phenotypes in 25 patients with retinal vasculitis*

Patient	*Diagnosis*	α_1 *AT (g/l) serum level*	α_1 *AT phenotype*
1	Sarcoidosis	2·1	M1M2
2	Idiopathic	3·3	M1M1
3	Idiopathic	1·6	M M
4	Idiopathic	2·1	M1M1
5	Behçet's syndrome	2 7	M1M1
6	Idiopathic	2·4	M1M2
7	Behçet's syndrome	1·8	M1M3
8	Behçet's syndrome	2·8	M1M1
9	Behçet's syndrome	2·2	M2M3
10	SLE	2·1	M1M2
11	SLE	3·6	M1M1
12	Idiopathic	2·5	M1M1
13	Behçet's syndrome	2·7	M1M1
14	Idiopathic	2·3	M3M3
15	Behçet's syndrome	1·7	M1M1
16	Behçet's syndrome	2·6	M1M3
17	Behçet's syndrome	3 0	M1M3
18	Idiopathic	2·5	M1M1
19	Idiopathic	2·8	M1M1
20	Idiopathic	1·7	M1M1
21	Idiopathic	2·8	M1M1
22	Idiopathic	2·3	M1S
23	Idiopathic	1·9	M1M2
24	Idiopathic	3·1	M1M2
25	Idiopathic	2 7	M1M1

Table 2 α_1 *Antitrypsin phenotypes in 25 cases of retinal vasculitis*

Aetiology	*No of patients*	*% Phenotype*			
		MM	*MS*	*MZ*	*MS and/or MZ*
Idiopathic	14	93	7	0	7
Behçet's syndrome	8	100	0	0	0
SLE	2	100	0	0	0
Sarcoidosis	1	100	0	0	0
Controls	339	89	7	4	11

Twenty-six alleles have been described for Pi. Each phenotype is described by a letter of the alphabet with M, S, and Z being the most common. Each phenotype has a distinct pattern on isoelectric focusing with polyacrylamide gel. Heterozygous individuals—for example, PiMZ—have both M and Z bands, while homozygous individuals such as PiMM or PiZZ have only a single M or Z band. PiMM is the commonest, occurring in 90% of the population. The remaining 10% of phenotypes are associated with a variable decrease in Pi levels.[15]

There were no deviations from the normal frequency of deficient phenotypes in 25 patients examined (Table 2). One patient had the MS phenotype. There were no patients with homozygous deficient phenotypes.

Discussion

α_1 antitrypsin is an important regulatory protein, acting as an inhibitor of serine proteases with activity against a large range of enzymes such as trypsin, leucocyte neutral proteases, collagenases, elastin, thrombin, kallikrein, and sperm acrosin.[16] It has the highest serum concentration of any protease inhibitor, and this combined with its low molecular weight (55 000) allow it to achieve very high concentrations in both intra- and extracellular compartments. Pi also is an important acute phase reactant, and it is this aspect of its activity that may be reduced in patients with deficient Pi phenotypes.[6]

The results of the present study indicate the capacity of serum α_1 antitrypsin to act as an acute phase reactant, with raised serum levels being present in the majority of patients with active RV. Serum α_1 antitrypsin may provide a useful marker of disease activity in patients with RV, as other parameters such as the ESR are usually normal in patients with this disease.[7]

Previous investigations have revealed an association between deficient phenotypes of α_1 antitrypsin and another important inflammatory eye disease, anterior uveitis.[3,17] This finding has not been universal, and several groups have failed to substantiate this observation.[18,19] These discrepant findings may be the result of a number of variables including Pi phenotyping techniques, population characteristics, or the failure of several authors to correlate the Pi phenotype with disease severity. Similarly, we have previously reported the lack of association between patients with deficient phenotypes of α_1 antitrypsin and posterior uveitis and a separate and smaller group of patients with RV.[3]

In keeping with observations in other immune mediated inflammatory disease and vasculitis syndromes such as SLE it was expected that patients with retinal vasculitis would show an increased frequency of α_1 antitrypsin deficiency, but this was not the case. A deficient α_1 antitrypsin phenotype was present in only one patient in the present study and in contrast to earlier findings in patients with anterior uveitis this subject did not have a more severe disease. Similarly, in contrast to previous studies, neither patient with SLE had a deficient α_1 antitrypsin phenotype. α_1 Antitrypsin deficiency has not been reported in association with Behçet's syndrome, and the results in this small group of patients show a lack of association with this disease. The results of the present study indicate significantly increased serum levels of α_1 antitrypsin in patients with RV but a normal distribution of α_1 antitrypsin phenotypes.

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Retinopathy of prematurity: review of a four-year period

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SUMMARY For a four-year period the development of retinopathy of prematurity (ROP) was determined among neonates considered at risk of acquiring this condition. Fifty-six out of 249 premature infants developed some degree of ROP. Comparison of these infants with a group of 56 controls, admitted to hospital in the same period and matched for sex, birth weight, and gestational age, showed significant differences for sepsis, blood transfusions, and the period of oxygen monitoring in relation to the period of oxygen administration. The most consistent factor associated with the development of ROP was gestational age at the time of birth, though no gestational age group was entirely devoid of ROP. This suggests that screening for ROP should not be restricted to high-risk premature infants only.

During the last decade retinopathy of prematurity (ROP) has often been discussed in clinical paediatric papers.[1 2] Improvements in technology now enable neonatologists to keep alive more neonates of very low birth weight (VLBW) and short gestational age. But although the opportunities for monitoring arterial oxygen tension have also improved, they have not stopped ROP from recurring. Its aetiology remains unknown. We studied the incidence of ROP in a four-year period and evaluated a number of risk factors in its pathogenesis.

Patients and methods

PATIENTS

From 1 April 1977 to 31 March 1981 678 premature neonates were referred to the neonatal intensive care unit of the Wilhelmina Children's Hospital. Eye examinations were performed as soon as the babies' condition permitted them to be transferred from intensive care to the intermediate care ward.

We examined the following children: (a) all those born at a gestational age of under 32 weeks; (b) neonates of 32 and 33 weeks' gestation who had received more than 40% oxygen for longer than one day or who had been artificially ventilated; (c) premature infants of 34 or more weeks' gestation on artificial ventilation or high oxygen concentrations over a longer period.

ROP cases were matched with control patients of the same sex, birth weight, and gestational age admitted to hospital in the same period. If a child with ROP was one of identical twins of which the other one did not develop ROP, the latter served as control (three cases). We thus examined 249 surviving premature infants. ROP was present in 56 (22·8%).

METHODS

Throughout the study period all premature infants receiving any supplemental oxygen were given 10 mg vitamin E/kg body weight on admission and subsequently once a week until the oxygen treatment was discontinued. The oxygen concentration in the inspired air was measured by Hewlett-Packard oxygen meters or set by the oxygen-blenders on the artificial ventilation apparatus (Bourns BP 200).

During the first two years of the study Pao_2 samples were drawn from all indwelling arterial lines at least once every four hours. This was continued during the last two years of the study, during which additional information was gathered by measuring transcutaneous Po_2 ($Ptco_2$) in as many children as long as possible (with a Hellige-Dräger electrode). Every two weeks children were selected for ophthalmic investigation according to the criteria mentioned above. Optimal mydriasis could be obtained in most

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children by giving them tropicamide and phenylephrine HCl 5% alternately every 10 minutes for 1½ hours. After the application of a local anaesthetic a baby-eyelid widener (Heiss) was introduced and indirect monocular ophthalmoscopy performed.

Follow-up investigations were performed as frequently as judged necessary in cases of proliferative ROP (until treatment or regression) or once every two weeks until discharge.

Results

ROP was found in 56 children out of 249 investigated (Table 1). General characteristics and some relevant clinical data of the ROP group and of the 56 non-ROP controls are given in Table 2. Data relating to oxygen administration and monitoring are presented in Table 3.

The ROP stages found in our patients, according to the Patz's modification[3] of Reese *et al.*'s classification (using RLF for retrolental fibroplasia)[4] were: pre-RLF in 23 (41·1%), grade 1 in 23 (41·1%), grade 2 in 7 (12·4%), and grades 3–5 (cicatricial forms leading to blindness) in 3 (5·4%). Fig. 1 shows the distribution of ROP cases in relation to the total of surviving premature infants and clearly points to an increasing risk with decreasing gestational age.

Table 1 *Series of 551 surviving premature infants (out of 678 admissions) from which ROP and control cases have been selected*

	n	*Examined*	*(% of n)*	*ROP*	*(% of examined cases)*
<32 wks	169	156	(92·3%)	43	(27·6%)
32–33 wks	122	73	(39·8%)	8	(11·0%)
>34 wks	260	20	(7·7%)	5	(25 0%)

Discussion

The link originally suggested between oxygen and ROP has been challenged, as Silverman stated in 1982,[5] and our study also casts doubt on it. Tables 2 and 3 show that in our ROP and non-ROP groups there are no significant differences between artificial

Table 2 *General characteristics and clinical data of 56 ROP cases and controls*

	ROP	*Non-ROP*
n	56	56
Mean gestational age (wks)	28·7	28·9
Mean birthweight (grs)	1140	1135
Male female	27 29	27 29
Artificial ventilation (n)	26	31 NS
Mean duration of ventilation (days)	15·6	14·5 NS
Patent ductus arteriosus	12	15 NS
Bronchopulmonary dysplasia	11	15 NS
Pneumonia	7	5 NS
Sepsis (proved by blood culture(s))	19	8* $p<0·05$
Exchange transfusion (number of children)	10	3* $p=0·06$
Mean number of blood transfusions in first two months	6 8	4,7† $p<0·005$

*χ^2 test
†Student's *t* test
NS = not significant.

Table 3 *Data pertaining to oxygen administration and monitoring*

	1 Apr 1977–1 Apr 1979		*1 Apr 1979–1 Apr 1981*	
	ROP	*Non-ROP*	*ROP*	*Non-ROP*
n	20	20	36	36
Mean duration of $\geq$40% O_2 administration (days)	19	17	14·9	11
Monitoring:				
None	12	8	7	2* $p=0·09$
arterial	8	12	3	4 NS
arterial + $Ptco_2$	—	—	8	11 NS
$Ptco_2$	—	—	18	19 NS
Mean no of Pao_2 measurements $\geq$100 mmHg	2 7	4,3	1·94	3·11 NS
Mean max Pao_2 (mmHg)	113	108	138	142 NS
Mean no of $PtCO_2$ measurements $\geq$100 mmHg	—	—	2,7	4·3 NS
Mean max $PtCO_2$ (mmHg)	—	—	108	114 NS
Duration of monitoring.				
Duration of suppl O_2 administered (>40%)	—	—	0 54	1,14† $p<0$ 01

*χ^2 test
†Student's *t* test

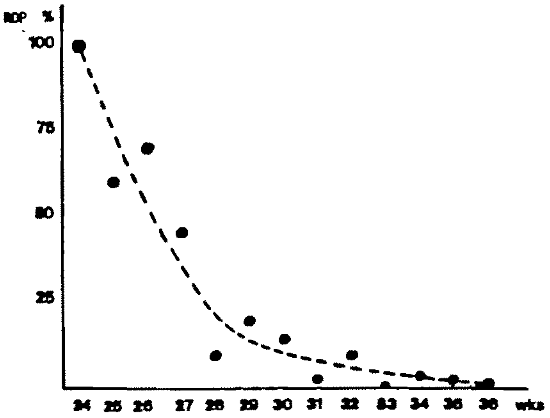

Fig. 1 *Incidence of ROP as a percentage of survival according to gestational age.*

ventilation and its duration, patent ductus arteriosus, bronchopulmonary dysplasia, mean duration of supplementory oxygen administration, and arterial and transcutaneous oxygen monitoring. Table 3 also shows that the introduction of $Ptco_2$ measuring has at least had a beneficial effect with regard to the mean duration of oxygen administration, which has decreased from 19 to 14·9 days in the ROP group and from 17 to 11·0 days in the control group.

That oxygen cannot be eliminated as one of the important factors in ROP may be derived from the fact that a significant difference was found between the study group and the control group in the duration of monitoring. When dividing the duration of monitoring (either arterial and/or transcutaneous) by the number of days supplementary oxygen was administered (≥40%), children from the ROP group were found to have been monitored for a significantly shorter time than those from the non-ROP group (ratios 0·54 and 1·14 respectively, Table 3).

Two other findings from our study may leave the oxygen theory at least partly intact. The first, the difference between exchange transfusions and blood transfusions between the two groups has been observed before[6-8] and widely discussed. The second, although seeming not directly to point to oxygen, is the difference in sepsis incidence. This finding has been reported before[9-12] but has evoked little comment.

It is our impression that the sepsis incidence may relate to the number of blood transfusions required in the neonatal period. In our patient groups there were no significant differences in number of children on artificial ventilation (and its duration) and number of children with arterial lines, which makes it unlikely that the difference in the number of blood transfusions was caused by increased blood sampling. However, increased haemolysis during sepsis periods may offer an explanation. With regard to oxygen radicals, it is now recognised that the oxidative burst which follows the activation of the superoxide generating systems occurs earlier and easier in newborn than in adult neutrophils.[13 14] When this mechanism operates throughout the whole body, and therefore also in the immature tissues and vessels of the eye, a link is established between sepsis with increased ocular toxicity and increased need for blood transfusions. On the basis of this concept we believe other investigators should consider sepsis as a possible risk factor in the development of retinopathy of prematurity.

The incidence of ROP in our patient population is comparable to the incidence mentioned by other authors in recent years.[15 16] The differing figures in different gestational age groups (<32 weeks: 27·6%, 32–33 weeks: 11%, and ≥34 weeks: 25%) may be the result of the selection criteria we used. The increasing risk with decreasing gestational age, probably the most consistently encountered risk factor for ROP in the literature, is also seen in our data (Fig. 1).

However, the finding that among our premature infants no gestational age group is devoid of ROP raises the question of the need for *all* premature infants to be seen by an ophthalmologist. For higher risk groups, in all those centres providing neonatal intensive care, this should be mandatory in our view. For lower risk groups, it seems necessary to define a moment of optimal timing for ROP diagnosis. This would seem to be somewhere between the 5th and 10th week after birth, because those studying children from birth have rarely encountered ROP *for the first time*[16 17] before or after this period.

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Anisometropia in children: analysis of a hospital population

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SUMMARY In a hospital population of 1356 children 64 (4·7%) cases of anisometropia (at least 2 dioptres in spherical or cylindrical power) were found. After the exclusion of all children with ocular lesions 53 remained. Twenty-seven (42%) of them had strabismus, which seemed to be related to accommodation effort rather than amount of anisometropia. Amblyopia was present in 17 (53%) of the patients with orthotropic anisometropia. Amblyopia increased with the amount of anisometropia. Therapy in the form of spectacle correction and part-time occlusion was successful in 47%. The success rate was related to the age of presentation.

In the developing human eye anisometropia is considered to be a causal factor in the pathogenesis of amblyopia and strabismus. It is believed that 6 to 38% of all cases of amblyopia are caused by anisometropia without strabismus,[1 2] whereas in about 12 to 18% of the children with strabismus this is accompanied by anisometropia.[2-4]

However, data on the prevalence of anisometropia and its complications in children are rare and divergent. The aim of this retrospective study was therefore to determine in a hospital population: the prevalence of the different forms of anisometropia, the prevalence of amblyopia or strabismus in combination with anisometropia, the changeability of anisometropia, and the results of treatment of anisometropic amblyopia.

Patients and methods

The archives of the Rotterdam Eye Hospital were screened for the records of anisometropic children born in 1972. Anisometropia was defined as a difference of 2 dioptres or more in spherical or cylindrical power between both eyes as determined by cycloplegic streak retinoscopy under either atropine 0·5% or cyclopentolate 1%.

For children up to 6 years of age written instructions were given to all parents on how to instill 0·5% atropine drops two hours prior to their appointment and twice daily for the preceding two days. In older children 1% cyclopentolate drops were used: two drops with 5-minute interval 30 minutes prior to retinoscopy. The following data were recorded: age and reason for presentation, type and degree of anisometropia, best corrected visual acuity, ocular alignment, monocular fixation pattern, and accompanying signs or cause of anisometropia.

Five types of anisometropia were distinguished: anisohypermetropia, anisomyopia, mixed astigmatism, anisoastigmatism, and antimetropia. Patients were classified according to their most ametropic eye. The axis of any cylindrical component was classified as with-the-rule if the minus cylinder axis was within 15° of 180°, against-the-rule for minus cylinder within 15° of 90°, or oblique (i.e., other than with-or against-the-rule). The degree of anisometropia was expressed in spherical equivalents.

According to Jackson's suggestion[5] not only the mathematical difference between the refraction of the two eyes but also the proportional difference was determined. The proportional amount of anisometropia was expressed in the ratio: anisometropia versus ametropia of the most emmetropic eye (for example, RE: −5 dioptres SE and LE: −3 dioptres SE proportional amount of anisometropia 2/3). In accordance with the child's maturity visual acuity was measured by using either picture targets, E hooks, or Snellen letters.

Since the results found on one scale are not quite comparable with those found on another, the amount

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of amblyopia and the improvement in vision under therapy have been expressed in a ratio using the visual acuity of the best eye as the denominator. Amblyopia was defined as visual acuity <1·0 (6/6) in the less good eye in combination with a ratio of 0·50 or less (e.g., visual acuity 1·5 (6/4) OD and 0·3 (6/20) OS, ratio 0·3/1·5). An improvement in vision of the amblyopic eye that increased the ratio 0·2 or more was considered a therapeutic success.

Wilcoxon's two-sample rank sum test was used to test significance.

Results

In January 1983 the archives of the Rotterdam Eye Hospital contained the records of 1356 children born in 1972. From these cases 64 cases of anisometropia (as defined previously) were obtained (4·7%). Anisometropia ranged from 0·25 to 7·25 dioptres spherical equivalents. Forty-five had anisohypermetropia, 13 anisomyopia, and six mixed astigmatism. Cases of pure astigmatic anisometropia (i.e., only cylindrical differences) or antimetropia were not found.

With the exception of four all cases of anisohypermetropia and anisomyopia had an astigmatic component. The minus cylinder was with-the-rule in 42, against-the-rule in five, and oblique in four patients, while in nine cases a combination was found.

Thirty-one patients first visited the Eye Hospital because of a (suspected) reduced visual acuity, 29 because of strabismus, and the remaining four for other reasons—namely, buphthalmos (2 cases), limbal dermoid as part of Goldenhar's syndrome, and trauma. There was an equal distribution between girls and boys.

The course of anisometropia was determined on the basis of data from all patients without ocular disease who underwent at least three retinoscopies (n=27). In this connection the follow-up ranged from two to eight years, with a mean of four years.

The amount of anisometropia in spherical equivalents remained constant in 18 children, increased in five (mean 1·25 D, range 0·75 to 2·25) and decreased in four (mean 1·25 D, range 0·75 to 1·5). In other words anisometropia (as defined previously) arose in one and disappeared in another child.

After ophthalmological examination 27 patients were found to have strabismus, that is, 24 children with esotropia and three with exotropia. The remaining 37 patients had orthotropia as determined in the cover test by the absence of a fixation shift. However, since the monocular fixation pattern was not always mentioned in the record it could not be used as a standard to exclude cases of microtropia, as defined by Helveston and Von Noorden.[4]

Table 1 *Comparison between children with orthotropic and heterotropic anisometropia*

	Straight (n=32)	*Strabismus (n=21)*	
Hypermetropia	21	19	
Myopia	7	0	
Mixed astigmatism*	4	2	
With-the-rule	22	14	
Against-the-rule	1	2	
Oblique	2	1	
Combination	3	4	
No astigmatism	4	0	
Amount of anisometropia	2·44±0·50†	1·95±0·42	p>0·1
Amount of ametropia of the most emmetropic eye	2·12±0·56	3·03±0·86	0·05<p≤0·1
Proportional amount of anisometropia	1·77±0·66	1·16±0·46	p>0·1
Age of presentation	5·53±0·72	3·38±0·74	p≤0·001

*Cases of pure astigmatic anisometropia or antimetropia were not found

†Mean ±2 SEM.

After the exclusion of all cases with ocular disease—namely, macular dystrophy cases, Brown's tendon sheath syndrome 2, buphthalmos 2, tilted disc, vascular anomaly in the macula, Goldenhar's syndrome with limbal dermoid, keratoconus, and keratoconjunctivitis scrofulosa—the orthotropic and heterotropic groups were compared with each other (Table 1). The two groups differed as to type of anisometropia, degree of ametropia of the most emmetropic eye, and age of presentation.

ORTHOTROPIC ANISOMETROPIA

Thirty-two patients had orthotropic anisometropia without ocular disease. All of these children except two had a difference in best corrected visual acuity between both eyes. Amblyopia as defined previously was present in 17 of them and always occurred in the more ametropic eye. The group with amblyopia differed from the 15 other children in the amount of anisometropia (0·1<p≤0·02), which was greater in the former (mean ±2 SEM: 2·98±0·76 and 1·52±0·54 dioptres spherical equivalents respectively). No significant difference could be demonstrated in the age of presentation, proportional amount of anisometropia, or amount of ametropia of the most emmetropic eye.

Amblyopia was treated with part-time occlusion (i.e., from waking until 4 pm) of the dominant eye preceded by the wearing of a spectacle correction for at least two months. In two patients occlusion therapy had to be abandoned because of non-cooperation.

Under this regimen 11 children showed improvement in visual acuity of the amblyopic eye. Eight of

Table 2 *Therapy results in anisometropic amblyopia*

Patient	*Age of presentation*	*Amount of anisometropia*	*Ametropia of the most emmetropic eye*	*Proportional amount of anisometropia*	*Visual acuity of the amblyopic eye*	*Ratio*	*End visual acuity*	*Ratio*	*Result**
1	4	2·25	3·25	0·75	0·25 (6/24)	0·3	0·25 (6/24)	0·25	F
2	2	4·0	2·0	2·0	0·5 (6/12)	0·5	0·7 (6/8·6)	0·7	S
3	3	4·0	4·25	1·0	0·1 (6/60)	0·1	1·0 (6/6)	1·0	S
4	5	1·75	0·75	2·25	0·3 (6/20)	0·3	1·0 (6/6)	1·0	S
5	9	5·0	1·5	3·25	0·5 (6/12)	0·5	0·5 (6/12)	0·5	F
6	6	3·75	0·25	15	0·5 (6/12)	0·5	0·5 (6/12)	0·5	F
7	6	3·25	2·0	1·5	0·2 (6/30)	0·2	0·4 (6/15)	0·4	S
8	6	1·25	0·75	1·75	0·3 (6/20)	0·3	0·25 (6/24)	0·2	F
9	2	3·75	1·0	3·75	0·5 (6/12)	0·5	1·0 (6/6)	0·65	F
10	9	2·0	6·0	0·25	0·5 (6/12)	0·4	0·6 (6/10)	0·5	F
11	9	2·0	1·25	1·5	0·5 (6/12)	0·5	0·8 (6/7·5)	0·5	F
12	4	3·0	3·75	0·75	0·3 (6/20)	0·3	0·8 (6/7·5)	0·5	S
13	3	1·75	2·25	0·75	0·3 (6/20)	0·3	0·8 (6/7·5)	0·65	S
14	8	7·25	1·0	7·25	0·25 (6/24)	0·35	0·4 (6/15)	0·5	F
15	6	0·5	1·75	0·25	0·5 (6/12)	0·5	0·8 (6/7·5)	0·5	F
16	6	2·5	3·0	0·75	0·5 (6/12)	0·5	1·25 (6/4·8)	1·0	S
17	6	2·75	1·0	2·75	0·5 (6/12)	0·5	1·0 (6/6)	0·85	S

*F=failure. S=success

them fulfilled the criteria of a therapeutic success, including one who was treated with a spectacle correction alone. Unfortunately, however, in three children the price of success was an occlusion-induced strabismus requiring surgical correction. The successful group differed from the other children only in regard to age of presentation $(0{\cdot}05<p\leq 0{\cdot}1)$, mean age 4·37±1·05 and 6·55±1·63 respectively (mean ±2 SEM). No difference was found in the amount of anisometropia, proportional amount of anisometropia, or ametropia of the most emmetropic eye (Table 2).

Discussion

In this study of a hospital population of 1356 children a prevalence of anisometropia of 4·7% was found. In a similar population of 5225 children 15 years of age and younger Phelps and Muir[2] found a prevalence of 4%. However, they defined anisometropia as a difference of 1·5 dioptres spherical equivalents or greater. It was also not clear whether or not cycloplegic retinoscopy was used. Ingram[7] found a prevalence of 2·7% in a general population of 1648 1-year-old children. Anisometropia was defined as a difference of at least 1 dioptre in spherical or cylindrical power.

Laatikainen and Erkkila[8] found a prevalence of 3·6% in 411 non-selected school children aged 7 to 15 years. They defined anisometropia as a difference of at least 1 dioptre spherical equivalent. Ingram[7] also described a highly significant association between anisometropia, hypermetropia, and astigmatism. This fits in with our experience. Of the 64 patients with anisometropia 45 had anisohypermetropia, while 60 had an astigmatic component.

Very little is known about the stability or changeability of anisometropia in the developing human eye. A hypothetical process of emmetropisation was postulated long ago by Straub.[9] However, many questions remain: does such a process actually exist or is it a mathematical artefact? Is it controlled by genetic or environmental factors,[10] for instance, the wearing of spectacles? And is it a monocular or binocular process?

This study suggests that anisometropia is a rather stable condition. Although changes in the amount of anisometropia did occur, they were small and might be partly due to interobserver variation, since not all retinoscopies were performed by the same person. Ingram *et al.*[11] recorded the appearance and disappearance of anisometropia (i.e., a difference of at least 1 dioptre in spherical or cylindrical power) between the ages of 1 and 3½.

In 27 children anisometropia was accompanied by strabismus (42%). Phelps and Muir[2] found this combination in 39% of cases. In the strabismus group the amount of ametropia of the most emmetropic eye was greater than that in the orthotropic group. This is in agreement with Phillips,[12] who showed that the better eyes of non-squinting anisohypermetropes were significantly less ametropic than those of the squinting anisohypermetropes. In combination with the findings that myopia was not present in our strabismus group, that almost all children had esotropia, and that neither the amount of anisometropia nor the proportional amount of anisometropia differed from the orthotropic group, this suggests that the presence of strabismus is related to the accommodation effort rather than the anisometropia per se.

Almost all children with orthotropic anisometropia had a difference in best corrected visual acuity between both eyes, but about half of them had amblyopia, i.e., 17 out of 32 (53%). By excluding all patients who did not meet Phelps's[2] definition of amblyopia—namely, a difference of two lines or more on the Snellen chart or less than 0·5 vision in one eye—and anisometropia our figures are in close agreement with those found by him, 15 out of 25 (60%) and 79 out of 132 (60%) respectively.

The finding that amblyopia always occurred in the most ametropic eye is in agreement with data of other authors.[1] The observation that the amblyopic and 'normal' groups differed with respect to the amount of anisometropia supports the findings of Kivlin and Flynn,[13] who demonstrated a positive correlation between the amount of anisometropia and the depth of amblyopia.

Under our therapeutic regimen eight patients (47%) with amblyopia were cured (therapeutic success). Sen's success rate was 64%.[14] When his definition of anisometropic amblyopia (namely, anisohypermetropia, orthotropia, and visual acuity in the amblyopic eye of ≤0·5) and therapy success (namely, improvement of at least 2 lines on the Snellen chart) were used, our success rate becomes 69% (9 out of 13). Kivlin and Flynn's success rate was 70%.[13] When their definitions of anisometropic amblyopia are used (namely, orthotropia and visual acuity in the amblyopic eye of less than 0·5) and therapy success (namely, endvision ≥0·5 (6/12)), our success rate becomes 50% (4 out of 8).

In our opinion it is preferable to use a certain improvement in vision rather than an end vision of 0·5 (6/12) as a criterion of success. The effect of measurement variation on the success rate is reduced, and it becomes possible to include cases with a visual acuity of 0·5 (6/12) in the amblyopic eye. Although several prognostic factors have been identified or suspected, such as age, depth of amblyopia, amount of anisometropia, therapy compliance, and accuracy of the optical correction, we could detect only the effect of age on our success rate.

In comparison with the results of other authors[13 15 16] our percentage of occlusion induced strabismus was high—i.e., 3–10% versus 20% (3 out of 15). Unfortunately, however, these authors do not describe their method of patching.

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Bilateral superior oblique palsies

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SUMMARY Eighteen consecutive cases of bilateral superior oblique palsy have been studied retrospectively. The patients were typically adults with a history of severe head trauma. All patients complained of diplopia, either vertical, torsional, or both. Other neurological sequelae were common. Central disruption of fusion was seen in three patients. Eight patients underwent surgery for torsional or vertical diplopia, and the results are briefly discussed.

Bilateral superior oblique palsy is not a common ocular motility problem.[1-3] It is nearly always acquired, often following closed head trauma, as in a road traffic accident. It is not unusual for the period of unconsciousness to be rather prolonged, and other neurological complications may occur. These patients complain of vertical diplopia, often with a torsional component, in the lower fields of vision, and are often orthophoric in the primary position. Fells and Waddell[4] have emphasised that this may cause delay in diagnosis and a tendency to label patients as 'compensation neurosis.' Careful examination, however, will reveal the defect, although several tests may prove necessary. A number of authors have emphasised that these palsies are often asymmetrical and may be misdiagnosed as unilateral acquired superior oblique palsy, and managed accordingly.

Patients and methods

Patient selection The charts of private patients attending the Children's and Strabismus Clinic at the Bascom Palmer Eye Institute between April 1974 and February 1983 were reviewed. Eighteen patients were found to have a diagnosis of bilateral superior oblique palsy and data from them were analysed. Of the 18 patients 13 were males and 5 females. The age range of the males was 19 to 71 years, mean 40, and of the females 24 to 74, mean 39.

Aetiology. Sixteen patients had suffered severe head trauma with loss of consciousness. Fourteen had been involved in a road traffic accident, one fell off a horse, and one was involved in an aeroplane accident. One patient had myasthenia gravis with a positive edrophonium test, but a poor response to oral pyridostigmine. One patient had probably had a long-standing right superior oblique palsy of the congenital type, on which was superimposed an acquired left superior oblique palsy of probable vascular aetiology. In the cases with closed head trauma the duration of unconsciousness, where known, was from half an hour to one month. There was a higher incidence of other traumatic neurological symptoms in patients whose coma lasted for two weeks or more. The duration of time between the initial trauma and being seen at the Bascom Palmer Eye Institute was known in 16 cases and ranged from two to 60 months, mean 22·5 months.

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Results

Clinical findings (Tables 1 and 2). All the patients complained of diplopia, either vertical, torsional, or in combination. Additional complaints included abnormal head position and headaches. Corrected visual acuities were good, the worst recorded being 6/12, and in no patient was there more than one Snellen line difference between the two eyes.

Ocular deviation. In four patients there was orthophoria in the primary position, and in two more the primary position deviation was purely horizontal. In the remaining 12 patients there was a vertical deviation in primary position. In five patients this was purely vertical, in one there was a coexistent esotropia, and in six there was an exotropia. In downgaze all patients showed an increase in the vertical deviation. In depression to either side nine showed a classical pattern of hypertropia of the adducted eye with diplopia reversing between left and right depression. In two cases this information is not available in the patient's record. In the remaining

Table 1 *Preoperative data*

Case	*Age, sex*	*Corrected VA*		*Presenting complaint*	*Aetiology*	*Other neurological problem*
		R	*L*			
1	31 M	6/3	6/3	Vertical diplopia	Myasthenia gravis	Positive edrophonium test
2	51 M	6/9	6/12	Torsional diplopia	Airplane accident Oct 1973 Head trauma	Amnesia
3	34 M	6/4	6/4	Vertical diplopia	Car accident Mar 1972. Head trauma	L hemiparesis R facial palsy L XI n palsy
4	43 M	6/6	6/6	Oblique diplopia	Car accident 1973 Cranioplasty 9 mo later	Field defect Retraction convergence nystagmus
5	26 F	6/9	6/12	Torsional diplopia	Car accident 1978. Head trauma	None
6	36 F	6/6	6/6	Headache Vertical diplopia	Fell off horse 9 months before Head trauma	Memory loss Depressed skull fracture R temporal area
7	47 M	6/6	6/6	Vertical diplopia	Car accident June 1977 Head trauma Coma 'days'	R hemiparesis Hearing loss Expressive aphasia
8	62 M	6/4	6/6	Vertical diplopia	Prob. 'congenital' RSO palsy+acquired LSO palsy 2° to hypertension	Meningioma of R convexity removed 1975
9	24 F	6/6	6/6	Vertical diplopia	Car accident Nov 1979. Head trauma Coma 3 days	None
10	74 F	6/9	6/9	Vertical diplopia	Car accident June 1980. Head trauma	None
11	24 M	6/6	6/6	Oblique diplopia	Car accident 1976 Coma 1 month	Weakness R arm Slurred speech L facial palsy
12	26 M	6/6	6/6	Torsional and vert diplopia Head tilt L	Car accident Apr 1981. Head trauma. Coma 2–3 wks.	L hemiparesis. Poor memory On phenytoin Abnormal speech
13	32 M	6/4	6/4	Oblique diplopia	Motorcycle accident July 1980 Head trauma Coma 3 wks	R hemiparesis Dysphasia
14	71 M	6/6	6/6	Vertical diplopia	Car accident Mar 1982 Head trauma. Coma 'days'	None
15	39 M	6/6	6/6	Oblique diplopia	Car accident Nov 1978 Head trauma Coma 2 wks	Poor balance Poor memory Nerve damage R foot
16	38 F	6/4	6/4	Vertical diplopia Chin depression	Car accident May 1982. Head trauma Coma ½ h	None
17	19 M	6/4	6/4	Vertical and torsional diplopia	Car accident Oct 1982. Head trauma Coma 48 h	None
18	25 M	6/4	6/4	Oblique and torsional diplopia	Car accident Oct 1978 Head trauma Coma 16 h	None

RSO=right superior oblique LSO=left superior oblique.

seven cases the paresis was judged to be asymmetrical, with one eye being constantly hypertropic, maximally in the opposite inferior field to the palsy.

Head-tilt test. The Bielschowsky head-tilt test was performed and recorded in 15 cases. In nine cases it was bilaterally positive, with upshoot of the eye on the side of the head-tilt. In six cases it was positive only on tilt to the more hypertropic eye, in all six cases the right eye.

Double Maddox rod test. The double Maddox rod test was used to measure subjective cyclodeviation. In 12 cases there was subjective excyclophoria which could be elicited on fixation with each eye. In three cases there was detectable excylophoria of only one eye, in each case the less hypertropic eye being the eye with the perceived cyclodeviation. In three cases the test was not performed.

Ocular rotations were assessed. In nine cases there was detectable underaction of both superior oblique muscles, often one more than the other. In seven cases only one superior oblique could be seen to underact, with overaction of the ipsilateral inferior oblique. In two cases the rotations were not recorded.

V pattern. Several authorities have emphasised the importance of a marked V pattern as an indicator of bilaterality in superior oblique palsies. In this series the size of the V pattern ranged from 30 prism dioptres to a small A pattern of two prism dioptres. In addition to the latter patient three others had no

Table 2 *Preoperative data*

Case	*Deviation primary position*	*Deviation in downgaze and R and L depression*			*'V' pattern*	*Bielschowsky head-tilt test*	*Cyclo-deviation*	*Rotations*	*Fusion?*
1	Ortho	8 LHT 4 LET	2 LHT 2 LET	2 RHT 4 ET	8	Positive to R and L	Bilateral excyclophoria	U/A LSO O/A LIO	Yes
2	Ortho	4 RHT 10 ET	20 ET	8 LHT 8 ET	20	Positive to L and R	5° Ex L 5° Ex R		Yes
3	45 LHT 10 XT	55 LHT 7 LXT	40 LHT 10 XT		15		20° Ex R 5° Ex L	U/A LSO O/A LIO	Dubious prob. absent.
4	18 RHT 10 ET	8 LHT 20 ET	18 RHT 20 ET	35 RHT 10 ET	30			U/A both SO	No
5	3–4 RHT 12 XT	22 LHT	6 LHT (fixR) 4 RHT(fixL)	14 RHT	8	Positive to L and R	15° Ex L and R	U/A both SO	Yes
6	14 RHT	10 RHT	18 RHT	30 RHT	0	Positive to R	10° Ex R 5° Ex L	U/A RSO O/A RIO	Yes
7	10 ET	12 ET 20 LHT	16 ET 4 LHT	12 ET 10 RHT	16		10° Ex R 12° Ex L	U/A both SO	Weak but present
8	2–3 RHT		10 RHT		8	Positive to R	5° Ex R 5° Ex L	Minimal U/A both SO	Yes
9	4–6 LHT	18 LHT	8 LHT	Ortho	0	Positive to L more than R	5° Ex R	U/A LSO O/A LIO	Yes
10	2–3 RHT 4 XT	1–2 LHT	15 ET 7 RHT	4–6 RHT	15	Positive to R more than L	Marked ex R and L	U/A both SO	Yes
11	30 RHT 7 XT		35 RHT 16 XT		−2 ('A' pattern)	Positive to R		U/A RSO U/A RLR	Unclear
12	5 RHT 3 XT	6 RHT	10 RHT 7 ET	12 RHT	19	Positive to R and L	10° Ex R 5° Ex L	O/A RIO	Yes
13	4 XT Trace LHT	2 XT 2 LHT	4 XT 2 RHT	4 XT 3RHT	0	Positive to R			Yes
14	6 RHT	3 RHT	12 RHT	18 RHT	8	Positive to R	10° Ex R 5° Ex L	U/A SO L more than R	Yes
15	Ortho	5 LHT 16 ET	3 LHT 20 ET	7 RHT 14 ET	20	Positive to R and L	4° Ex R 7° Ex L	U/A both SO	Yes
16	5 RHT 1 XT	8 RHT 3 ET	10 RHT 1 ET	8 RHT 3 ET	2	Positive to R and L	11° Ex L	U/A RSO	Yes
17	Ortho	2 RHT 8 RET	5 RHT 10 RET	6 RHT 6 RET	10	Positive to R	5° Ex L	U/A both SO	Yes
18	1–2 RHT 3 XT	8 LHT 12 ET	8 ET	16 RHT 12 ET	15	Positive to R and L	5° Ex R 15° Ex L	U/A both SO O/A both IO R more than L	Yes

ET=esotropia, convergent squint XT=exotropia, divergent squint HT=Hypertropia. All measurements are in prism dioptres except where otherwise indicated

detectable V pattern. In the 14 cases with a V pattern the average was 18 prism dioptres, and only in three cases was it 20 or more prism dioptres.

Fusion was assessed by tests in free space and, where doubt existed, on the synoptophore. Fourteen patients had good fusion when corrected with prisms or on the synoptophore. One had poor fusion, two had no fusion, presumably owing to head trauma, and in one case the fusional status was unknown.

Other neurological problems. Eight patients had no neurological signs or symptoms (one had coincident hypothyroidism). One patient was myasthenic. Nine patients had significant sequelae of their head trauma (summarised in Table 1). These ranged from memory loss after temporal skull fracture to hemiparesis, dysphasia, and convergence-retraction nystagmus. As might be expected, all the cases with absent, poor, or doubtful fusion had major neurological problems.

MANAGEMENT

Non-surgical management. This was advised in seven cases. The reasons were various. One case (No. 1) had myasthenia gravis and only moderate symptoms. One case (No. 5) was already improving spontaneously when first seen and continued to do so. Two cases (Nos. 9 and 10) had small deviations which could be rendered tolerable by prisms or occulsion of one lens of reading glasses. Three cases (Nos. 4, 11, and 13) with major neurological problems were advised that surgery would probably not be of value in relieving their symptoms, and one of these was fitted with prisms.

Surgical management. Table 3 shows the surgery

Table 3 *Surgery and results*

Case	*Date of surgery (interval from onset of palsy)*	*Surgery performed*	*Immediate postop status*	*Final postop status*	*Rotations*	*Success*
2	17 May 74 (7 months)	Bilateral superior oblique tucks		6/6 both eyes Diplopia in extreme gaze positions RHT3–4 in up and R gaze LHT2–3 in down and L gaze	Mild U/A LIO	Yes
3	(1) 13 Sept 73 (2) 15 July 74 (3) 21 Oct 74 (18 months)	(1) LIO Recession, RIR recession 6 mm (2) Bilateral superior oblique tuck (3) RLR recession 8·5 mm, LSR recession 3 mm, LIR resection 4 mm		(1978)-Still diplopia. 25 LHT distance, 8 RHT near Poor vertical OKN	Limited upgaze R more than L	No
6	20 Aug 79 (1 year)	Right superior oblique tuck	12–14 LHT 15° incyclo Fusing in lower field of gaze	(1979)-Diplopia only on up and downgaze at distance Primary position 3 EP+1 LHT Large field of single vision	U/A RIO	Yes
7		Bilateral superior oblique tucks 10 mm R, 12 mm L	Diplopia all fields of gaze. A exotropia Bilateral incyclo 50° L, 20° R	(1982)-Intermittent diplopia-can control. 2 LHT near and dist 5° incyclo Bilateral 'Brown's'	U/A bo IO	Partial
12	26 Apr 82 (1 year)	Bilateral Harada-Ito procedures. R inferior oblique disinsertion	Incyclo 2° R Primary 8 XT 7 LHT Downgaze 8 XT 6 LHT	Small field of single vision with 2 prism dioptres BDR $\left.\begin{array}{l}\text{with 2 prism dioptres BU}\\ \text{with 1 prism dioptres BO}\end{array}\right\}\text{L}$		Partial
14	(1) 22 Nov 82 (2) 23 May 83 (8 months)	(1) R superior oblique tuck (2) L inferior rectus adjustable recession	Improved Still diplopic	Less diplopia Primary-ortho $\begin{matrix}\text{3 LHT}\\ \text{4 ET}\end{matrix}$—2 RHT—$\begin{matrix}\text{6 RHT}\\ \text{3 ET}\end{matrix}$	O/A RIR U/A LIR	Partial
16	14 Mar 83 (10 months)	R inferior oblique recession L adjustable Harada-Ito	Better Little incyclo			Yes

ET=esotropia, convergent squint. XT=exotropia, divergent squint HT=Hypertropia All measurements are in prism dioptres except where otherwise indicated

performed and the results in seven patients. One patient is awaiting surgery elsewhere (No 15), and three patients are awaiting surgery in Miami (Nos. 8, 17, and 18). Various surgical treatments have been given. In all cases some form of superior oblique strengthening operation was performed, either unilaterally or bilaterally. Two cases (3 and 14) required multiple surgical procedures. Few conclusions could be drawn from these data, though it is notable that the patients with the best results from surgery had relatively mild injuries as judged by the absence of other neurological problems. On the other hand the patients who had poor results in terms of freedom from diplopia had all suffered considerable trauma. All had had a hemiparesis and other serious neurological sequelae of their injury. Whether the poor result can be attributed directly to the fusion loss or to the motility defect is unclear.

Discussion

Bilateral superior oblique palsies are not very common. Rucker[1,2] in his two separate series of 1000 cases of third, fourth, and sixth nerve paralyses found incidences of 67 out of 1000 and 84 out of 1000 for acquired fourth nerve palsy, but did not examine for bilaterality. This was done in a very similar study by Rush and Younge,[3] also from the Mayo Clinic. They found 172 out of 1000 cases of fourth nerve palsy, of which 13 were bilateral, 12 being considered to be due to head trauma. Younge and Sutula[5] reported 52 cases of superior oblique palsy over a two-year period. This included all causes of superior oblique palsy, including congenital palsy. They found four bilateral cases, all traumatic. Burger *et al.*[6] reported on 33 patients of superior oblique palsy, four of whom were bilaterally affected. All were the result of severe head injury, with coma lasting for 16 hours to 13 days. One of their patients, a 7-year-old boy, improved spontaneously, but the other, adult, cases did not. Khawam *et al.*[7] reviewed 3000 consecutive cases of strabismus and found 40 cases of acquired superior oblique palsy, of which seven were bilateral. Sydnor *et al.*[8] reported 33 cases of traumatic superior oblique palsy over a 10-year period. Of these, 12 were thought to be bilateral.

Other authors have reported series of bilateral superior oblique palsy. Chapman *et al.*[9] reported six cases, all due to motor car accidents. Raskind[10] reported three cases, all post-traumatic. Hermann[11] reported nine cases initially diagnosed as unilateral which turned out to be bilateral after the initial surgery was performed. Lyle[12] reported eight cases seen over a five-year period, all traumatic in origin. Mitchell and Parks[13] reported nine patients in a prospective study of superior oblique surgery. The largest reported series of which we are aware is that of Fells and Waddell,[4] who reported 31 patients, 25 of whom were the result of head trauma. The present 18 cases were found on review of approximately 5500 patient case notes and covered a nine-year period.

Many authors emphasise the necessity of suspecting bilaterality in all cases of traumatic superior oblique palsy. This is touched upon by Khawam *et al.*[7] and Sydnor *et al.*[8] Hermann[11] devotes his entire paper to nine cases initially thought to be unilateral which showed paresis of the opposite side after the initial surgery. Various diagnostic criteria are advised; Sydnor *et al.*[8] suggested that a V pattern of more than 25 prism dioptres, excyclotorsion of more than 10°, or head trauma sufficient to cause loss of consciousness should suggest possible bilaterality. Our figures do not suggest that a V pattern should exceed 25 prism dioptres, our average being 18, with four patients showing no V pattern whatsoever. In addition the cases reported by Hermann[11] had an average V of 6·5 prism dioptres, one case having an A pattern. In a series of six patients reported on by Chapman *et al.*[9] only four had significant V patterns. None of Raskind's three patients had a V pattern.[10] All but one of Michell and Parks's patients had a V pattern, but the size is not given.[13] Fells and Waddell[4] do not report the incidence of V patterns in their series.

We seem to be on safer ground when examining cyclotorsion. A number of patients complained of torsional diplopia, and double Maddox rod testing revealed excyclophoria in almost all patients. Ellis and Helveston[14] and Fells[15] have suggested that a finding of excyclotorsion of more than 15° by this method is strongly suggestive of bilateral fourth paresis. The average in this series was 13° of excyclotorsion. In very asymmetical cases the excyclophoria was perceived as being in only one eye, interestingly enough the less hypertropic in each case. This would seem to accord with the findings of Olivier and Von Noorden[16] in which the subjective tilt is seen in the non-dominant eye irrespective of the paresis. The only test used to measure torsion was a double Maddox rod test. Ruttum and Von Noorden[17] have recently thrown doubt on the usefulness of this test, especially when adjustable sutures are used on the superior oblique muscle. Fells and Waddell[4] advocate the use of a T-piece wand with a Lees screen as being accurate and non-fatiguing. The technique is described by Dulley and Harden.[18]

We agree with Sydnor *et al.*[8] and Fells and Waddell[4] that there is an association of bilaterality with severe head injury and with other neurological sequelae. It is also noted by Burger *et al.*[6] On the other hand Khawam *et al.*[7] state, 'the apparent insignificance of the head injury was a striking feature in many of the cases.' They do not specify whether they are discussing unilateral or bilateral cases. All the cases reported by Raskin[10] and Chapman *et al.*[9] were rendered unconscious, in several instances for prolonged period of time. It seems clear that severe head injury is much the commonest precipitating cause. The mechanism is less clear. Most authors, on anatomical grounds, place the lesion in the anterior medullary velum, where the trochlear nerves decussate. An alternative explanation is suggested by the work of Heinze[19] on fatal road traffic accidents. He found that the third, fourth, and sixth nerve could be wholly or partially avulsed as they emerged as rootlets from the brain stem.

When positive in both directions of head tilt, the Bielschowsky head tilt test is diagnostic. It will be positive in only one direction in very asymmetric palsies, and should not be relied upon when performed in the supine patient, as pointed out by Sydnor *et al.*[8] We therefore suggest that bilaterality should be suspected in all severe head injuries, that a Bielschowsky head tilt test may be diagnostic, and that the diagnosis be made on the basis of the deviation in major gaze positions, cyclotorsion measurements, and assessment of the ocular rotations.

As regards the results of surgical treatment, it will be seen that a variety of procedures were used, making it difficult to draw conclusions. We believe that it is insufficient in these cases to operate solely on the overacting muscles—that is, the inferior obliques or inferior recti. However, Lyle[12] in 1964 reported on eight patients in whom a variety of surgical procedures, including inferior oblique myomectomy and repositioning of the inferior rectus insertions, gave good results. Five of his patients in addition had superior oblique plications. In our view some form of superior oblique strengthening procedure must be performed, either plication or the Harada-Ito anterior half tendon transposition procedure. A good description of this procedure (modified by Fells) is given by Mitchell and Parks,[13] and illustrated in Fig. 1. If the excyclotorsion can be eliminated by this means, further surgery or prisms may be used to deal with any residual deviation. In general the better demonstrable fusion preoperatively, the better the surgical result. Fells and Waddell[4] have advised against being too influenced by apparent poor fusion, as this may be due to torsional diplopia, with improvement of fusion after surgery.

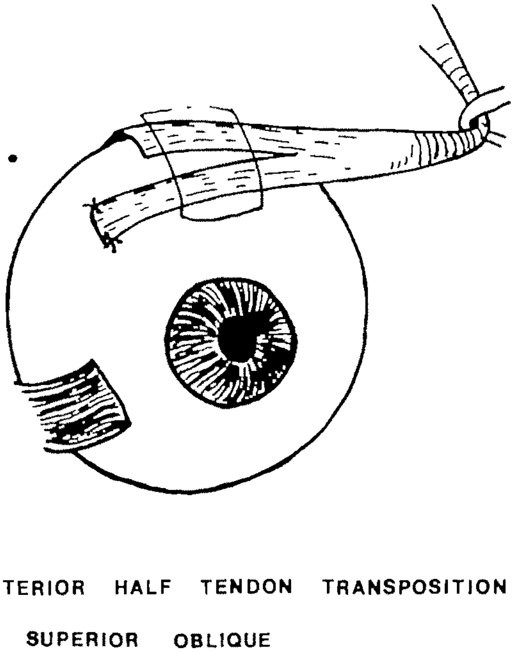

Fig 1 *Anterior and temporal transposition of the anterior portion of the superior oblique tendon improves the cyclotorsional action of the muscle.*

CONCLUSION

Bilateral superior oblique palsy is an uncommon but debilitating condition, usually a sequela of severe head trauma. Care in testing and a high index of suspicion are required to detect bilaterality in asymmetric cases. Loss of fusion may occur, but, where it is present, appropriate surgery with strengthening of the superior oblique muscles is the treatment of choice.

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Ring melanoma of the iris and ciliary body

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SUMMARY The case is described of a tumour of the iris and ciliary body—a ring type melanoma—primarily diagnosed and treated as pigmentary glaucoma.

Malignant melanoma of the anterior part of the uveal tract, spreading round the eyeball, is called ring melanoma.[1-8] The first case of such a tumour was described by Solomon in 1882 (quoted in Rockwell[6]).

The growth of a ring melanoma may begin in the anterior part of the ciliary body, in the iris, or in the iridociliary junction. The neoplasm spreads round the major arterial circle of the iris and along the ciliary muscle. Its growth towards the choroid may cause retinal detachment and imitate primary tumour of the choroid. Infiltration of the chamber angle causes secondary glaucoma. Heterochromia or even tuberosity of the affected iris may occur. The tumour spreading along the scleral blood vessels and nerves and along Schlemm's canal causes extrascleral growth, imitating primary melanoma of the bulbar conjunctiva.[1 2 5 7 9-11]

According to Rockwell 32 cases of ring melanoma of the ciliary body and iris had been reported up to 1952.[6] Later on further cases were added.[4 7-9]

Case report

A man aged 57 consulted an ophthalmologist in January 1983 complaining of some deterioration of vision in the left eye. Examination revealed visual acuity 6/8 with elevated intraocular pressure. There were a few pigmentary sediments on the corneal endothelium. The iris was blue, its structure normal, with pigment scattered on the surface. On the circumference of the lens initial opacification was observed. The fundus did not show any abnormalities. Gonioscopy showed a wide chamber angle, filled with pigment. Tonography by Grant's method gave 0·05. The field of vision was normal. The right eye showed amblyopia, visual acuity 2/60, without any other noticeable abnormalities.

Although the patient had been treated for three months with pilocarpine, timolol, phenylephrine, and acetazolamide, the intraocular pressure oscillated between 28 and 43 mmHg. Pigmentary glaucoma was diagnosed and trabeculectomy performed. The post operative course was uneventful and the pressure reduced to normal (14–17 mmHg). During the following seven months the patient had regular examinations, which did not reveal any further abnormalities in the operated eye.

Two months later the patient consulted the ophthalmologist again complaining of the pigmented changes noticed in the operated eye. He was admitted to the clinic with a diagnosis of intraocular malignant melanoma.

Examination showed almost normal visual acuity in the left eye and an intraocular pressure of 14 mmHg. Dispersed, brownish-black subconjunctival nodules grouped together in the medial angle of the eye were visible (Figs. 1, 2, 3). One of the nodules covered the limbus of the cornea at 11 o'clock, and three other nodules were located on the caruncle.

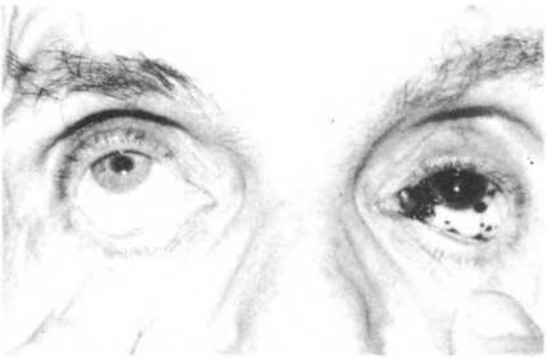

Fig. 1 *View of both eyes with hyperpigmented nodules and heterochromia of the iris in the left eye.*

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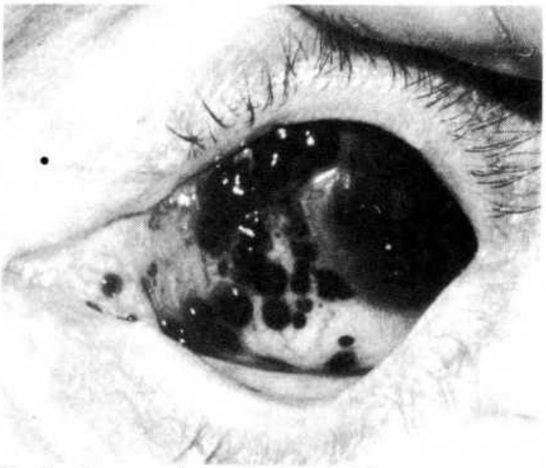

Fig. 2 *Numerous, brownish-black nodules varying in size, grouped in the medial angle of the eye. One of the nodules covers the limbus of the cornea.*

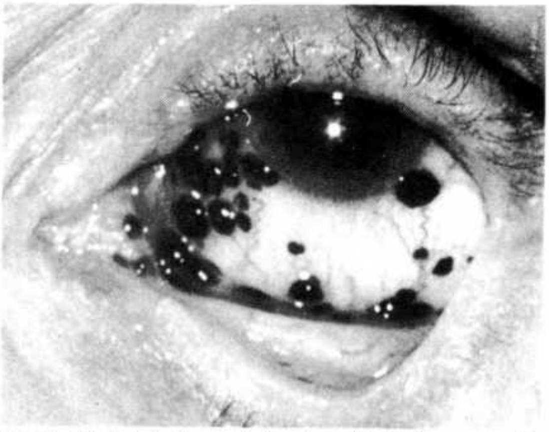

Fig. 3 *Nodules in the medial angle and in the lower part of the eyeball.*

Brown hyperpigmentation was visible on the conjunctiva and the margin of the lower lid. There were several pigmentary sediments on the corneal endothelium. The colour of the iris had changed to dark brown and its surface was nodular. The postoperative peripheral defect of the iris was two-thirds covered by a pigmented tissue. The lens showed initial opacifications at its periphery, with dispersed pigment on the surface. The optic disc was pale, with typical glaucomatous excavation. Gonioscopy showed a chamber angle of medium width, narrowed in some places and entirely filled with pigment. Scintigraphy with chromium ^{51}Cr labelled bleomycin revealed greater accumulation of the marker in the left eye. A general medical examination did not show any essential abnormalities, and the results of biochemical tests were unchanged. Radiographs of the thorax and the vertebral column, as well as scintigraphy of the liver and spleen, did not reveal any metastases. Under general anaesthesia the orbit was exenterated.

HISTOLOGICAL EXAMINATION

The specimen was divided into two parts, embedded in paraffin, and cut in serial sections. Microscopically a malignant neoplasm was seen which infiltrated circumferentially the whole iris and a considerable part of the ciliary body, occupying the chamber angle. It infiltrated the sclera with its vessels, spread-

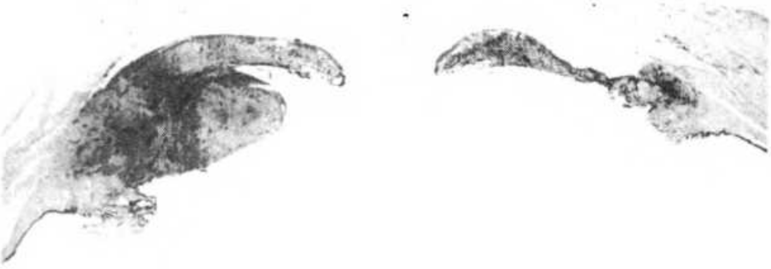

Fig. 4 *Malignant melanoma infiltrating circumferentially the iris and ciliary body.*

ing to episcleral tissues and conjunctiva, where numerous subepithelial nodules were formed (Figs. 4, 5, 6, 7, 8). The tumour cells were spindle-shaped or epithelioid-like, with oval polymorphous nuclei and irregular prominent nucleoli. Numerous cells contained a large amount of melanin. The individual cells or groups of cells were separated by a dense net of reticulin fibres. Posterior structures of the globe, the optic nerve, and soft tissues of the orbit were not infiltrated. The diagnosis was malignant melanoma of the iris and ciliary body (ring type melanoma), of mixed cellular type with a considerable amount of pigment and reticulin fibre. The resection lines were free of neoplastic infiltration.

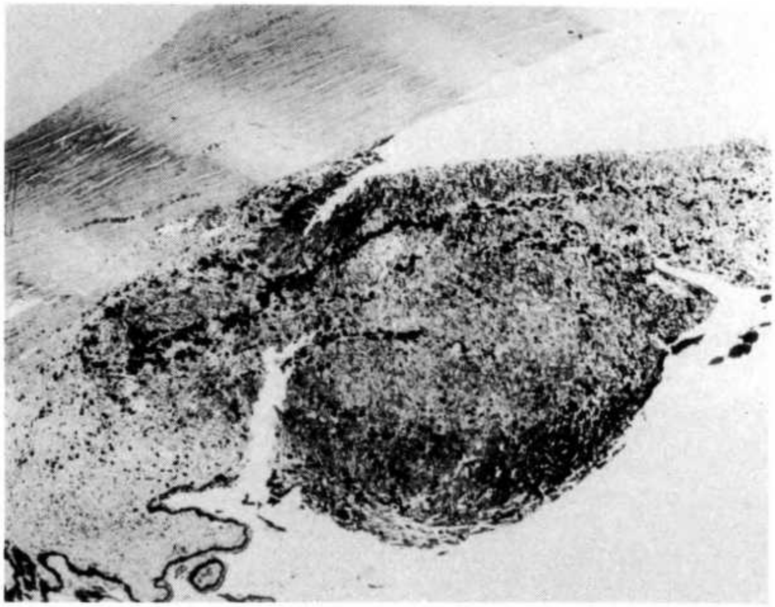

Fig. 5

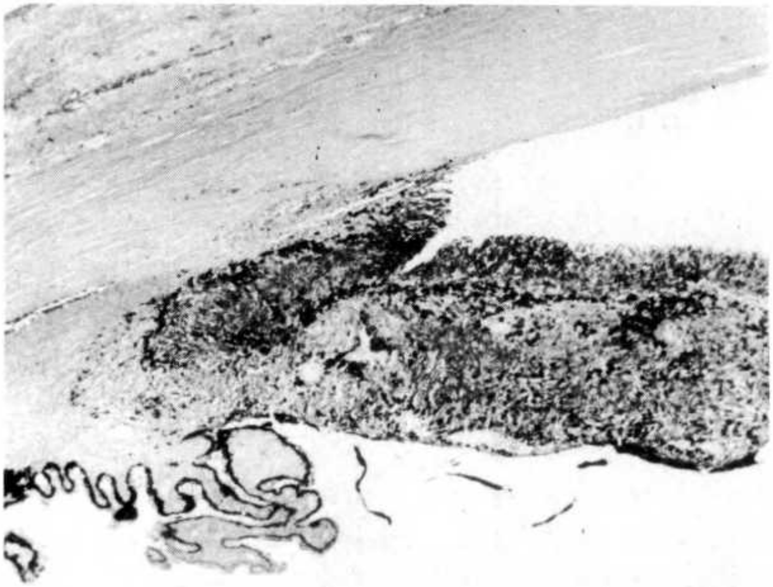

Fig. 6

Fig. 5 and 6 *The infiltration of the iris, the base of the ciliary body, and the region of the chamber angle by the melanomatous cells. Spread of the tumour along the communicating vessels in the sclera. (Haematoxylin and eosin, × 80).*

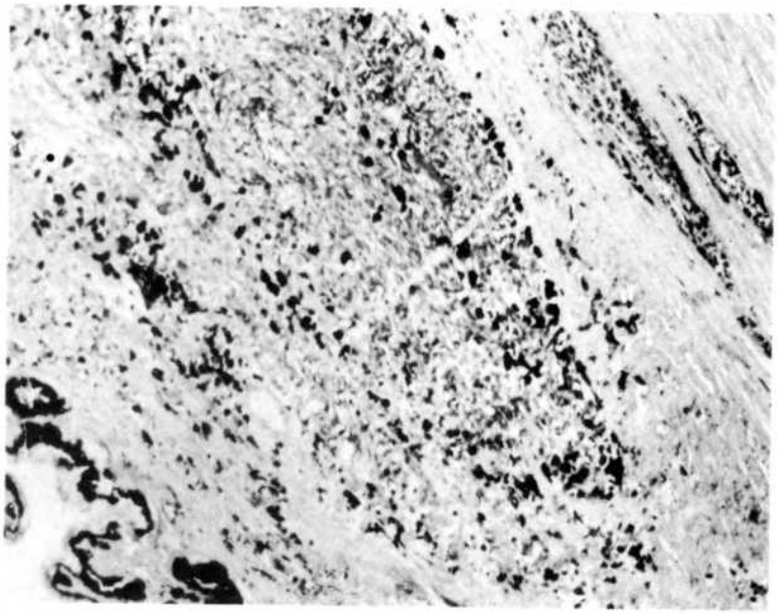

Fig. 7 *Solid melanomatous infiltration of the ciliary body and the dissemination of the neoplastic cells within the sclera. (H and E, × 150).*

Discussion

Reports have shown that in cases of ring melanoma the structures of the chamber angle and the outflow canals are almost always invaded, which leads to secondary glaucoma. Increased intraocular pressure may be the first symptom of a tumour, but such cases are frequently misdiagnosed and surgically treated as primary glaucoma, because the attention of an ophthalmologist is drawn to the increased intraocular pressure rather than to the slowly developing hyperpigmentation of the iris.[1 3 5–7 12]

In our case at first heterochromia was not observed, and gonioscopy did not reveal any signs of the tumour. Consequently pigmentary glaucoma[13 14] was diagnosed and antiglaucomatous surgery performed. Only after some months did the presence of dark nodules under the bulbar conjunctiva and iris heterochromia suggest the dissemination of malignant melanoma.

It should be remembered that ipsilateral glaucoma with even slight hyperpigmentation in the anterior part of the eye should arouse suspicion of melanoma. We believe that histopathological examination of the biopsy specimen removed from the iris during an antiglaucomatous operation would make a correct diagnosis possible.

Our patient was in his sixties, but a considerable

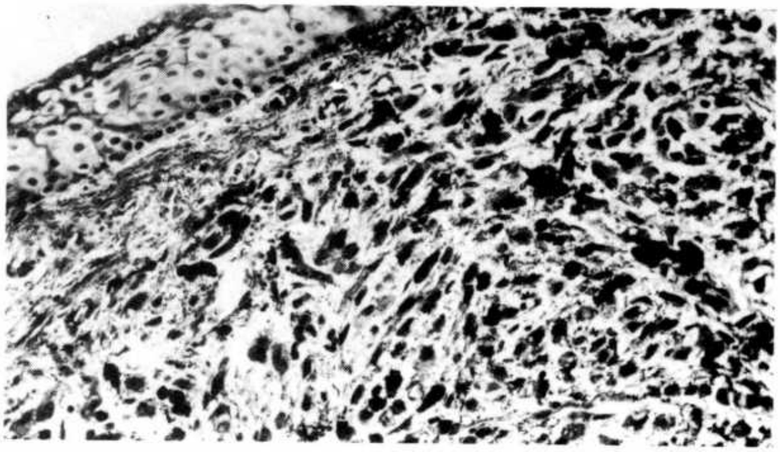

Fig. 8 *Malignant melanoma with heavily pigmented cells, infiltrating the conjunctiva and lifting its epithelium. (H and E, × 220).*

proportion of ring melanomas have been reported in people in the first two decades of their lives. So it should be kept in mind that youth is not a factor reducing the chance of developing a melanoma of this type. Many authors emphasise that melanomas of the iris, because of the possibility of their early detection and their usually spindle cell structure, have a better prognosis than choroidal melanomas.[15] However, the prognosis in our patient is doubtful because of subconjunctival dissemination of the tumour and its epithelioid cell component.

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An Alternative View...

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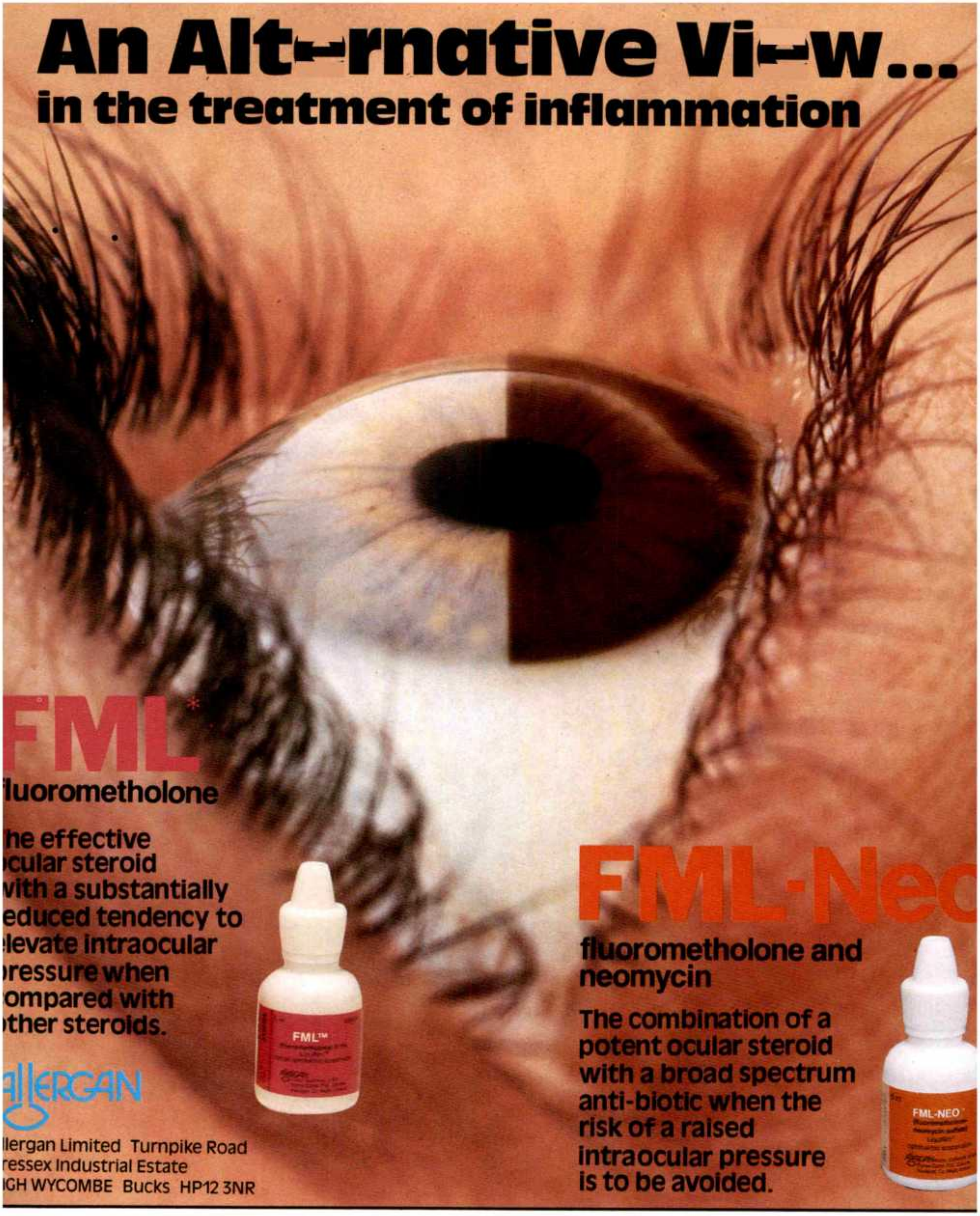

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ırs the dosage may be safely increased to 2 drops every hour. Care should be taken not to discontinue therapy prematurely.
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dary ocular infections from fungi or viruses liberated from ocular tissue. In those diseases causing thinning of the cornea or
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en of the age group two years or below. This preparation contains benzalkonium chloride and should be used with caution in
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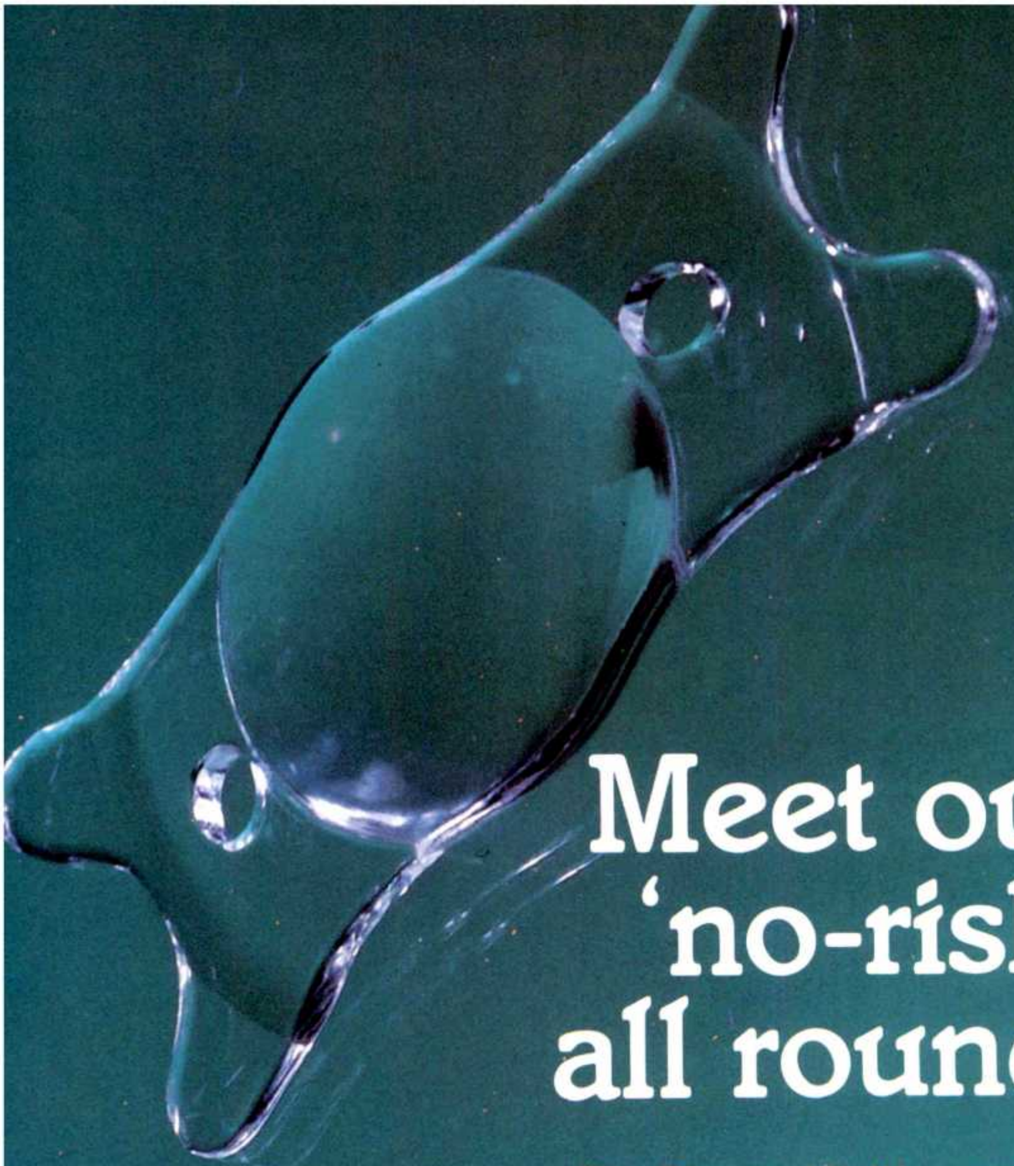

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Corneal sensitivity in myasthenia gravis

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SUMMARY Corneal touch thresholds were measured in 11 people suffering from myasthenia gravis (MG) and in a control group of 20 subjects. The mean threshold in MG was 75·6 mg (SD 52) and in the control group 18·9 mg (SD 7·3); thresholds were thus significantly ($p<0·01$) raised in MG. Although it is not possible to say whether the sensory deficit is due to MG or to the treatment, the results implicate acetylcholine in sensory transduction in the cornea.

The clinical picture in myasthenia gravis (MG) is well established, and has recently been reviewed by Grob.[1] The disease is characterised by weakness of skeletal muscles, especially those innervated by the cranial nerves. Sensory complaints of numbness and tingling are encountered in about 10% of cases, especially close to the onset of the disease. The incidence of the disease is about 1:20 000.

We were interested in a possible association between myasthenia gravis and corneal sensitivity because of the high cholinergic activity in the corneal epithelium[2,3] and its association with corneal innervation.[4,5] We therefore measured corneal touch thresholds in patients suffering from myasthenia gravis and found an abnormally high incidence of reduced sensitivity.

Materials and methods

Corneal sensitivity was measured with a Cochet-Bonnett aesthesiometer, filament diameter 0·12 mm (Lunneau et Coffignon, Paris) mounted in a holder attached to a slit lamp This allowed movement of the instrument in X, Y, and Z directions, permitting good control of the approach to the cornea. Subjects fixated a light 30° above the horizontal, and the filament of the aesthesiometer was applied normally to the cornea about 1 mm from the inferior limbus to minimise apprehension.[6]

Stimuli were applied to the cornea initially with the filament of the aesthesiometer extended to its maximum effective length (6 cm), which produces a force of 11 mg (area 0·013 mm^2). Six stimuli were applied at this length. The filament was shortened in 5 mm increments and 6 stimuli applied at each length until the subject responded (by pressing a buzzer) that the stimuli were felt.[7]

Blank stimuli were included to test for reliability. Threshold was taken as the filament length to which the subject responded 50% of the time. The procedure is preferable to one using suprathreshold stimuli, since these raise thresholds.[8] Data were converted to force (in mg) for analysis.

Subjects suffering from myasthenia gravis were referred to us by the MG Association of Australia. Clinical details are given in Table 1. We measured thresholds in a control group of 20 subjects, who were

Table 1 *Case details of subjects with myasthenia gravis*

Subject	*Age (yrs)*	*Medication*	*Duration of MG (yrs)*	*CTT (mg)*	
				RE	*LE*
1	26	Pyridostigmine	1·0	52	52
2	61	Pyridostigmine Prednisone	3·5	145	145
3	37	Pyridostigmine	6	36	36
4	65	Pyridostigmine	0·8	75	36
5	43	Pyridostigmine Prednisone	12	52	145
6	70	Pyridostigmine Prednisone Imuran	14	145	16
7	25	Pyridostigmine	3	100	145
8	56	Pyridostigmine Azathioprine	0·75	16	16
9	58	(Thymectomy)	19	16	13
10	36	(Thymectomy)	5	16	16
11	40	(Thymectomy)	3	12	13

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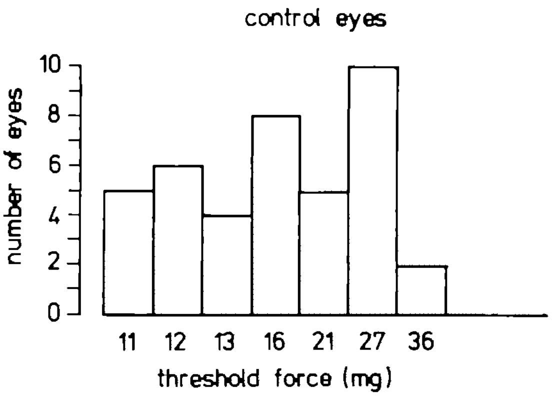

Fig. 1 *The distribution of corneal touch thresholds in 20 normal subjects, used as a control group in this experiment. The threshold force increments correspond to 0·5 cm decrements in the length of the aesthesiometer filament.*

untrained observers selected randomly from our general clinic. The age distributions of the two groups were similar (experimental group, mean 47·0 years, SD 15·7; control group, mean 44·6 years SD 13·9). The experimental group consisted of two brown eyed subjects, four green eyed, and five blue eyed. The control group consisted of nine brown, six green, and five blue eyed subjects. Therefore eye colour suggests that the control group should have less sensitive corneas than the experimental group, other factors being equal.[9] All subjects were free of visible corneal abnormalities, and none wore contact lenses. So far as we could establish, the eyelid musculature of the patients with myasthenia gravis functioned normally.

Results

The results of this study are summarised in Figs. 1 and 2. The mean corneal touch threshold (CTT) in myasthenia gravis was 75·6 mg (SD 52), while in the control group the mean threshold was 18·9 mg (SD 7·28); thresholds in myasthenia gravis were significantly higher than normal ($p<0{\cdot}01$). An inspection of Fig. 2 shows that the touch thresholds of myasthenia subjects were not normally distributed. They could be divided into two groups, one of which had normal sensitivity and the other markedly reduced sensitivity.

Discussion

Of the 11 subjects with myasthenia gravis three had been successfully treated by thymectomy and were currently free of problems without medication. These three subjects had normal corneal sensitivity. Of the other eight subjects five had sensitivity significantly below control levels in one or both eyes ($p<0{\cdot}01$, CTT 75 mg). It is possible that the control group in this study was abnormally sensitive. However, even if previously published control groups are used, these five cases are abnormally insensitive[8] ($p<0{\cdot}05$).

It is not possible to say whether the reduction in sensitivity in these cases is due primarily to the myasthenia gravis or to the treatment, since we did not examine any case prior to treatment. Nor is it possible to deduce the likely origin of the sensory deficit from our present understanding of sensory transduction in the cornea. Although a number of studies has revealed the corneal nerves to have cholinergic properties,[4,5,11] others have produced contradictory evidence.[12,13] The results of this study are consistent with the hypothesis that corneal sensory nerves have cholinergic properties, but do not provide conclusive evidence that transduction is mediated by acetylcholine.

Finally we note that, where the cornea is likely to be exposed to injury or infection, those who suffer from myasthenia gravis are at a greater risk than normal, suggesting that caution is required in these cases.

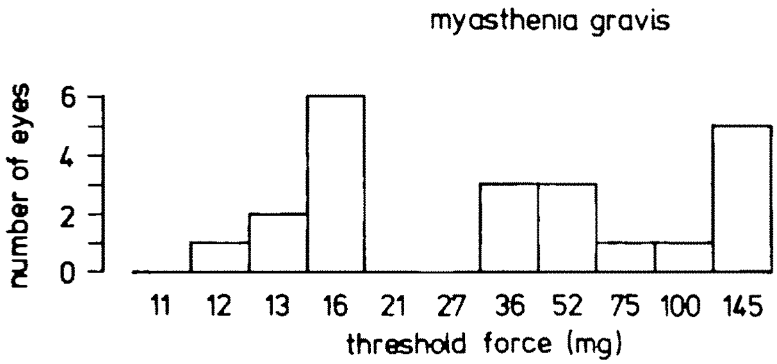

Fig. 2 *The distribution of corneal touch thresholds in 11 subjects suffering from myasthenia gravis Each eye is included as a separate point; for other details see Fig. 1.*

We are grateful to Mrs Tania Hoyle, MG Association of Australia, for organising subjects for this study

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Fundus flavimaculatus: polymorphic retinal change in siblings

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SUMMARY A 12-year-old boy and an 11-year-old girl, siblings of healthy, consanguineous parents, had a bilateral retinal dystrophy with a gradual loss of vision. The brother showed a bull's eye macular change with sparse fundus flavimaculatus type flecks. The sister had numerous fleck lesions of fundus flavimaculatus throughout the posterior fundus, but there was virtually no macular change. Thus the siblings presented instances of polymorphic expressivity of fundus flavimaculatus.

The classification of hereditary macular degeneration is based on knowledge of the genetic, morphological, and functional abnormalities, but controversy has existed on the identification of some disease conditions. If a polymorphic macular change is found among members of a given family, the abnormality probably indicates the variable expressivity of a genetically identical disease. We describe a pedigree in which two siblings of consanguineous parents showed bull's eye macular change with sparse fleck lesions of fundus flavimaculatus type and fundus flavimaculatus without macular involvement, respectively.

Case reports

The patients are a brother and sister who are two of three children of first-cousin consanguineous parents (Fig. 1). The parents and their youngest child, aged 9 years, were examined and found to be normal. Family members of the parents live in the southwest region of Kyushu island of Japan. None of the accessible relatives were willing to come for examination, but according to information obtained from the parents no other relatives are affected with any hereditary ocular disease.

CASE 1

A 12-year-old boy was born in 1972 after a uneventful delivery, and had been well in general health. He was referred to us for investigation of a gradual loss of vision; according to his history the visual acuity at 7 years was 0·8 in both eyes, followed by a gradual diminution. He complained of bilateral blurred vision, but had no photophobia. On examination the visual acuity was 0·1 in both eyes, which was not correctable with either glasses or contact lenses. There were no refractive errors. Goldmann perimetric tests showed in both eyes a dense central

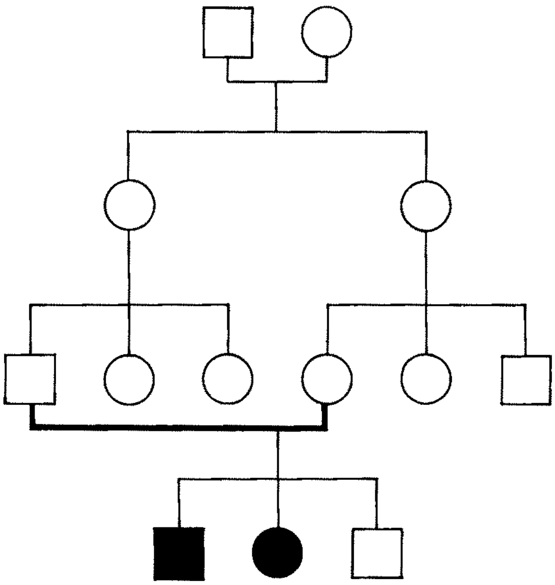

Fig 1 *Pedigree of the family*

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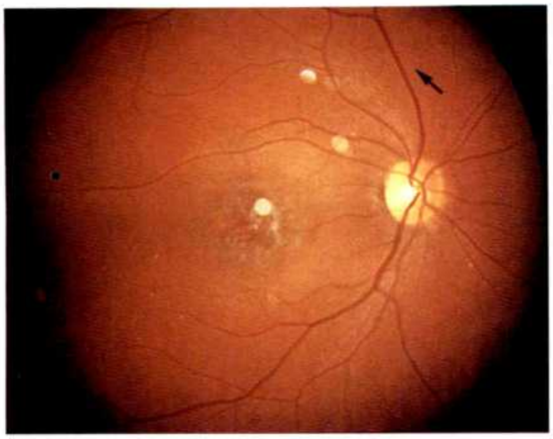

Fig. 2A

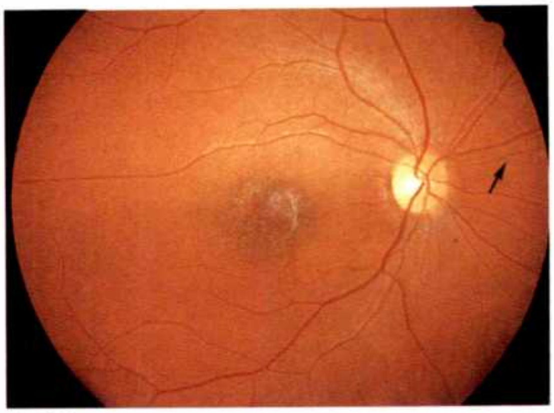

Fig. 2B

Fig. 2 *Right fundus of case 1 (brother).* (A) *April 1983*, (B) *June 1984. Bull's eye maculopathy. Arrows indicate fleck lesions of fundus flavimaculatus type.*

scotoma of about 10°, but the peripheral visual fields were normal. The Farnsworth panel D-15 test revealed a tritan defect, and the Farnsworth-Munsell 100-hue test showed a total error score of 188 with non-specific axis. He had no difficulty in night vision. The photopic and scotopic electroretinograms were normal. The ocular anterior segments and media were normal.

Ophthalmoscopic examination showed bilateral, symmetrical change of the macular region, in which there was a horizontal, oval, well defined atrophic lesion measuring 2 disc diameters in width and 1·5 disc diameters in height, having a beaten-bronze metallic appearance. A few yellowish white, ill defined flecks were deposited in the deep retina of the posterior fundus. The retinal vessels and optic discs were normal. The fluorescein angiograms revealed a dark choroid with a central ovoid zone of hyperfluorescence due to atrophy of the pigment epithelium, presenting a bull's eye macular change.

Follow-up observations 14 months later showed an increasing number of flecks of fundus flavimaculatus type, though they were not so conspicuous as in case 2. The bull's eye macular lesions remained unchanged (Figs. 2A, 2B, 3).

CASE 2

An 11-year-old girl, sister of case 1, was born in 1973 without any history of abnormality during gestation and delivery, and had developed well. She was referred to us together with her brother for investigation of a gradual loss of bilateral vision. She had no difficulty in night vision. On examination the refractions were normal, and the visual acuity was 0·1 in both eyes, which was not correctable with glasses. Goldmann perimetry showed in both eyes a small, weak central scotoma with normal peripheral fields.

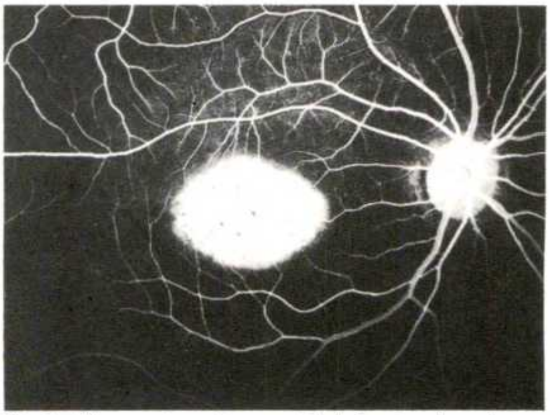

Fig. 3 *Fluorescein angiogram of right fundus of case 1 (June 1984).*

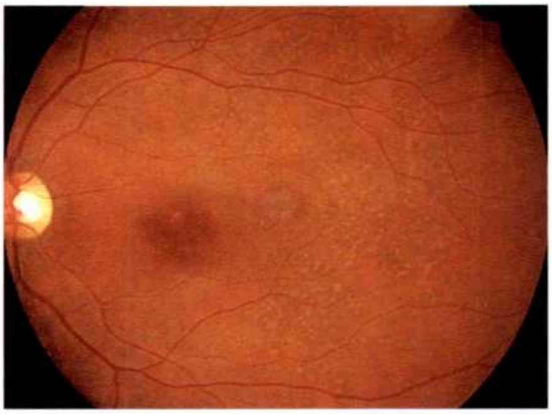

Fig. 4 *Left fundus of case 2 (sister). Fundus flavimaculatus.*

The Farnsworth panel D-15 tests showed a tritan defect, and the Farnsworth-Munsell 100-hue test revealed a total error score of 430 with non-specific colour confusion. The photopic and scotopic electroretinograms were normal. The ocular anterior segments and media were normal.

Symmetrical abnormalities were present in both eyegrounds. Numerous linear or fishtail-like, ill-defined yellowish white flecks were deposited in the deep retina throughout the posterior fundus. The macular region appeared normal, with an intact foveolar reflex, though there were minute pigment granularities. The retinal vessels and optic discs were normal (Fig. 4). Fluorescein angiographic study was recommended, but it was not accepted by the patient. Follow-up 14 months later showed no substantial changes in the fundus.

Discussion

It is evident that the siblings described above had a polymorphic dystrophic change in the retina.

The bilateral macular degeneration of one sibling, case 2 (sister), is consistent with fundus flavimaculatus, a term first introduced by Franceschetti[1] to describe an autosomal, recessively inherited, bilateral retinal degeneration in which white or yellowish white, round or linear ill-defined flecks are scattered in the deep retina of the posterior fundus with frequent association of macular degeneration.[2,3] This case is consistent with the 'pure form' of fundus flavimaculatus without macular involvement,[2,4] though minute pigment granularities in the fovea may suggest an early macular degeneration and account for the reduced visual acuity.

The bilateral macular change in case 1 (brother) is characterised by bull's eye lesions with a beaten-bronze atrophic appearance. The bull's eye macular change has been known to occur in a variety of hereditary retinochoroidal diseases, including cone dystrophy, central areolar choroidal dystrophy, Stargardt's disease and fundus flavimaculatus, and in chloroquine retinopathy. The relatively mild colour vision defect with no photophobia, a normal photopic electroretinogram, and well preserved choroidal vessels may exclude the diagnosis of cone dystrophy and central areolar choroidal dystrophy,[3-6] and chloroquine retinopathy is also excluded by the patients' history. Stargardt's disease is an autosomal, recessively inherited, juvenile macular degeneration, in which the macula is involved primarily, but white or yellowish white flecks similar to those found in fundus flavimaculatus are deposited frequently in the deep retina of the posterior fundus,[7,8] and those flecks were described in at least some of the patients of Stargardt's original report.[9] Although case 1 showed at the initial visit only a small number of faint fleck lesions, characteristic flecks became conspicuous and increased in number during a follow-up period of 14 months. So fundus flavimaculatus with macular involvement may be the correct diagnostic term for this case.

Since the siblings are children of consanguineous, healthy parents, it may be certain that their disease was caused by the same autosomal recessive gene, and their retinal change represents a marked polymophism in fundus flavimaculatus.

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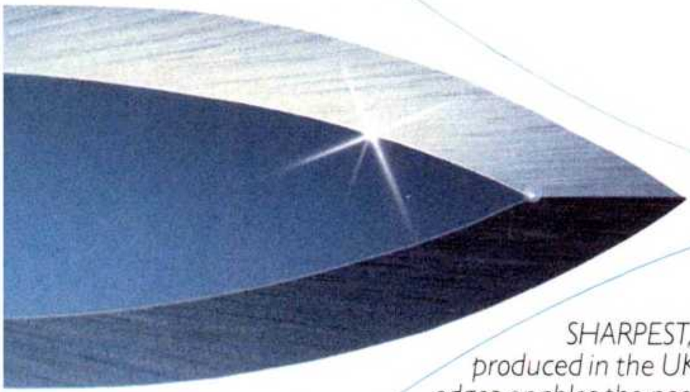

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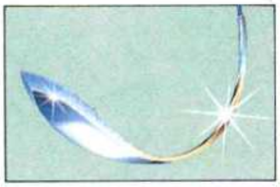

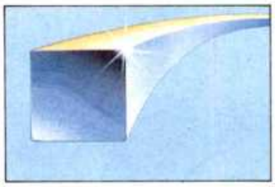

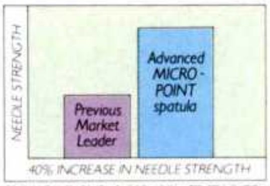

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British Journal of Ophthalmology, 1985, **69**, 525–528

Destructive epidemic *Neisseria gonorrheae* keratoconjunctivitis in African adults

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SUMMARY An epidemic of *Neisseria gonorrheae* keratoconjunctivitis in African adults occurred in Malawi in 1983. Sixteen patients, seven females and nine males, aged 18 to 60 years, were admitted to the inpatient ocular services at Queen Elizabeth Central Hospital in Blantyre from 1 February to 28 May 1983, all with severe bilateral purulent keratoconjunctivitis and concomitant venereal infection secondary to *N. gonorrheae*. Corneal melting, corneal perforation with iris prolapse, and endophthalmitis occurred in 10 eyes, of which five required enucleation. Thirteen additional eyes sustained severe visual loss secondary to corneal ulceration, leucomata, and healed corneal perforation. The route of transmission and factors of epidemicity are speculative. Because of worldwide epidemic venereal infection ophthalmologists and epidemiologists should be alert to probable sporadic *N. gonorrheae* epidemics in adults. Such outbreaks could occur elsewhere, especially in the developing world, and ocular gonococcal infection might become a significant cause of irreversible blindness.

External ocular infection secondary to the Gram-negative intracellular diplococcus *Neisseria gonorrheae* has been long recognised as a neonatal complication of venereally infected mothers.[1 2] Adult gonococcal ocular infection has been considered an uncommon disorder in relation to neonatal infection. With the recent rising worldwide rates of venereal disease adult ocular gonococcal infection has been increasing.[3-5]

There are certainly anecdotal accounts of *N gonorrheae* keratoconjunctivitis with corneal destruction and endophthalmitis in African adults, but thorough reports of this devasting ocular infection are scanty. In Malawi it has been reported and treated periodically at central and peripheral hospitals. An outbreak of ocular *N. gonorrheae* keratoconjunctivitis occurred in southern Africa in early 1983. Many adult patients with initial external purulent ocular infection and subsequent endophthalmitis, unconfirmed by laboratory diagnosis but believed to be secondary to *N. gonorrheae*, presented to hospitals other than Queen Elizabeth Central Hospital in Blantyre in 1983.

The following is a report of adult patients admitted to the services of the Department of Ophthalmology, Queen Elizabeth Central Hospital, with *N. gonorrheae* keratoconjunctivitis during 1 February to 28 May 1983.

Patients and methods

From 1 February to 28 May 1983 16 patients, nine male and seven female, were admitted as inpatients to the Department of Ophthalmology, Queen Elizabeth Central Hospital with acute, purulent conjunctivitis, clinically suspected to be *Neisseria gonorrheae*. In all but one case (7) the diagnosis was confirmed by laboratory determinations. The infection case unconfirmed in the laboratory behaved clinically like severe *N. gonorrheae* infection and went on to bilateral corneal perforation and iris prolapse.

The patients ranged in age from 18 to 60 years (18–60 in males, 21–31 in females) and initially sought medical attention at the general outpatient clinic of the ophthalmology services at Queen Elizabeth Central Hospital. Four patients (2, 13, 15, and 16) presented with bilateral corneal melting and perforation with iris prolapse (Figs. 1, 2). In all cases

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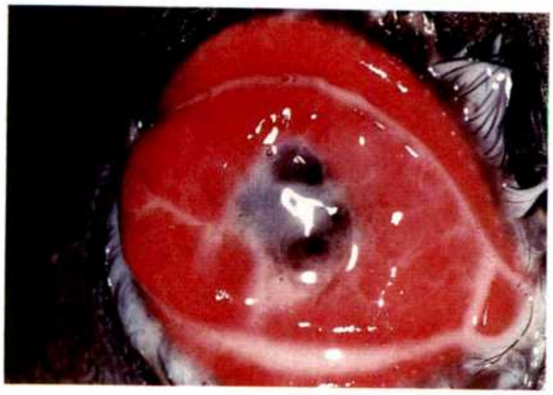

Fig. 1 *Patient 2, 60-year-old male. Acute* N. gonorrheae *keratoconjunctivitis with corneal destruction, OS.*

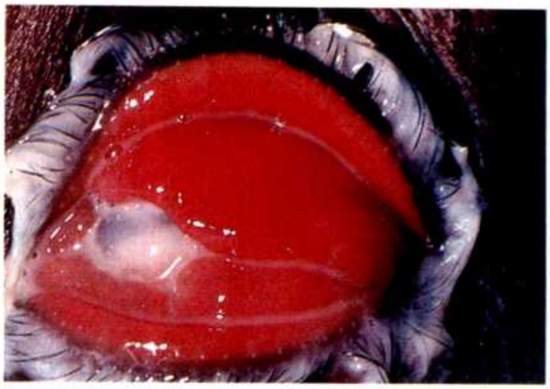

Fig. 2 *Patient 13, 30-year-old female.* N. gonorrheae *corneal perforation and endophthalmitis, OD.*

ocular involvement was bilateral and no patient reported any ocular disorder or injury prior to the onset of conjunctivitis.

Laboratory diagnosis was established by the presence of Gram-negative intracellular diplococci in Gram's stain and copious growth of *N. gonorrheae* on chocolate agar in 24 hours. The laboratory services were unable to assay for penicillinase-producing strains. All cultures were reported sensitive to penicillin.

Gram staining was performed on material from 15 of 16 patients and culture and sensitivity testing on material from five patients. (There are periodic shortages in culture media, which accounts for our not culturing all infections.) As previously noted, the diagnosis in one patient was established clinically, and neither culture and sensitivity testing nor Gram's staining were performed.

Results

History and physical examination revealed evidence of acute *N. gonorrheae* venereal infection in all sixteen patients.

Treatment for all the patients consisted of procaine penicillin 3·0 ml intramuscularly for nine days; crystalline penicillin eye drops (prepared and buffered by the pharmacy, Queen Elizabeth Central Hospital) to both eyes hourly for the duration of the hospital infection; atropine 1% drops to both eyes twice daily; and tetracycline 1% ointment to both eyes four times daily.

All the patients were confined in two isolation rooms to prevent cross infection to the 50-bed pre- and postsurgical ward.

Four patients were admitted with active corneal destruction, and of these eight eyes three developed endophthalmitis and were enucleated. In one patient corneal melting and endophthalmitis developed during inpatient treatment and necessitated enucleation. Another patient sustained bilateral corneal melting and perforation with iris prolapse while undergoing treatment and required bilateral scleral (covering) patch grafts. One patient developed a unilateral anterior staplyloma, which also required enucleation. Three patients sustained bilateral leucomata severely affecting visual acuity, and another patient, in whom the left eye had been enucleated, developed an axial leucoma in the right eye.

Of 32 normally-sighted eyes prior to infection only 14 retained visual acuity of 6/6 after infection had been treated and cleared. Five eyes were enucleated and seven were left with a visual acuity of 3/60 or worse in the involved eye.

Discussion

The occasional adult patient with bilateral acute purulent conjunctivitis secondary to *N. gonorrheae* had been treated by the ophthalmology staff at Queen Elizabeth Central Hospital, but those nurses and clinical officers with long experience (up to 23 consecutive years) on service at the hospital could not recall a previous epidemic of this extent. Most of the adult patients who had presented in past years for treatment of this ocular infection had appeared randomly. However, several staff members had noticed that the infection had been seasonal.

This epidemic coincided with the heavy rains in Malawi's tropical weather cycle. An annual seasonal outbreak of bilateral viral haemorrhage conjunctivitis coincided with the reported *N. gonorrheae* cases, but there is no proved relationship. Thousands of patients with viral haemorrhage conjunctivitis were treated in outpatient ophthalmic departments in

Table 1 *Epidemic* Neisseria gonorrheae *keratoconjunctivitis with corneal destruction and endophthalmitis in Malawi in 1983. Patients who were treated on the eye services at Queen Elizabeth Central Hospital in Blantyre are presented in the chronological order by which they were admitted*

Patient	*Sex*	*Age (years)*	*Home district*	*Date admitted*	*Diagnosis established by*	*Sequelae*	*Surgery required*	*Visual results*	
								OD	*OS*
1	F	31	Blantyre	1 Feb 83	Pos Gram stain Pos culture	None		6/6	6/6
2	M	60	Zomba	3 Feb 83	Pos. Gram stain Pos culture	Bilateral corneal perforations, iris prolapse, endophthalmitis	Enucleation OU	NLP	NLP
3	M	40	Blantyre	7 Feb 83	Pos Gram stain	None		6/6	6/6
4	M	22	Thyolo	7 Feb 83	Pos. Gram stain Pos culture	Bilateral leucomata		6/60	3/60
5	F	25	Chiradzulu	15 Feb 83	Pos. Gram stain	None		6/6	6/6
6	M	23	Zomba	17 Feb 83	Pos Gram stain	Bilateral leucomata		6/24	1/60
7	M	18	Zomba	2 Mar 83	Clinical diagnosis	Bilateral corneal perforation, iris prolapse	Scleral patch grafts, OU	6/60	6/24
8	M	27	Zomba	8 Mar 83	Pos Gram stain	Anterior staphyloma OD	Enucleation OD	NLP	6/6
9	F	30	Machinga	17 Mar 83	Pos Gram stain	Bilateral leucomata		6/24	1/60
10	F	19	Chiradzulu	17 Mar 83	Gram stain, Pos. culture	None		6/6	6/6
11	F	21	Mwanza	22 Mar 83	Pos Gram stain	None		6/6	6/6
12	M	25	Chickwawa	24 Mar 83	Pos Gram stain	None		6/6	6/6
13	F	30	Chiradzulu	30 Mar 83	Pos Gram stain	Bilateral corneal perforation, iris prolapse	Bilateral scleral patch grafts	3/60	6/60
14	M	40	Blantyre	9 May 83	Pos Gram stain	Endophthalmitis OS leucoma OD	Enucleation OS	3/60	NLP
15	M	23	Zomba	27 May 83	Pos Gram stain	Bilateral corneal perforations, iris prolapse, endophthalmitis	Enucleaton OS	6/6	NLP
16	F	30	Not Available	28 May 83	Pos Gram stain Pos. culture	Bilateral corneal perforations and iris prolapse	Scleral patch grafts, OU	2/60	3/60

NLP = no light perception

Malawi during January through April 1983. Viral haemorrhage conjunctivitis, though uncomfortable, is not known to cause corneal complications.

All the patients reported on here who presented with *N gonorrheae* conjunctivitis and keratoconjunctivitis were clinically venereally infected with the same organism. The route of transmission in assumed to be by contamination and through inadequate hand washing and hygiene in poor socioeconomic circumstances. Interviews for detailed histories of sexual contacts and practices were not undertaken, and it is not known if ocular infection occurred from direct venereal facial contact.

One can speculate about the possible relationship of the epidemic with wetter and more humid weather conditions during the heavy rainy season and possible water contamination through face washing. Ground water is more readily available for personal hygiene during the rainy season. Likewise the occurrence of the epidemic with acute bilateral viral haemorrhagic conjunctivitis might represent a second ocular pathogen, with secondary acute infection by *N. gonorrheae*. The factors which might have produced this epidemic, however many, are undefined.

The rising rates worldwide of venereal infection in general and *N. gonorrheae* in particular should alert the ophthalmic community to prepare for future outbreaks of this virulent and tragic blinding infection.

The authors gratefully acknowledge the assistance in patient management and compilation of records of Mr William Chagona, chief clinical officer in ophthalmology, sister-in-charge Mrs Towera Chipeta, of ward 4B, and sister Charlotte Gondwe, Department of Ophthalmology, Queen Elizabeth Central Hospital, Blantyre, Malawi

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Effect of intravitreal hyaluronidase on the clearance of tritiated water from the vitreous to the choroid

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SUMMARY The rate of transfer of intravitreally injected tritiated water from the mid vitreous to the choroid is significantly increased after depolymerisation of vitreous hyaluronic acid by injected hyaluronidase. The significance of this finding is discussed in relation to such conditions as retinal detachment and reattachment.

We have previously described a method for studying the transfer of intravitreally injected tracers from the vitreous to the choroid. The major proportion of intravitreally injected tritiated water is rapidly cleared to the choroid across the cortical vitreous, retina, and retinal pigment epithelium (RPE).[1] This movement of water from the vitreous to the choroid may be of importance in the maintenance of retinal apposition.[2 3] We were interested to see whether modification of the physical characteristics of the cortical vitreous gel by depolymerisation of its contained hyaluronic acid would alter the rate of transfer of tritiated water from the mid vitreous to the choroid.

Hyaluronic acid in the vitreous is an important structural component,[4] and, although this highly polymerised hydrophilic molecule is likely to interfere with bulk movement of water, it has been suggested that diffusional water movement would not be so influenced (Balazs E A, personal communication). In the present series of experiments we have measured the clearance of intravitreally injected ^3H_2O in rabbit eyes in which the vitreous hyaluronic acid had been deploymerised by previously injected hyaluronidase and have compared the results with earlier measurements on normal rabbit eyes.[1]

Materials and methods

The experiments were performed on a group of six adult male Dutch rabbits weighing between 1·6 and 2·4 kg and compared with control experiments carried out on a group of nine animals of similar strain, age, and weight. The animals were anaesthetised with intravenous ethyl carbamate (Urethane) in a dose of 1·9 mg/kg body weight. Subsequently 750 international units of bovine testicular hyaluronidase (Hyalase; Fisons Ltd, Pharamaceutical Division) in 0·1 ml water was injected via the pars plana ciliaris into the middle of the vitreous cavity of one eye with a microsyringe and a 26 gauge needle. The injecting needle was kept in situ during the rest of the experiment.

Approximately 30 minutes after the injection of hyaluronidase 25 µCi of ^3H_2O in 25 µl of water was injected into the mid vitreous through a separate injection site in the pars plana ciliaris, and this needle too was kept in situ while clearance of the injected ^3H_2O to the choroid was measured by the technique previously described.[1] In summary, the upper nasal vortex vein was identified, cleared of surrounding tissue, and divided. Blood was collected from its cut end into long form Pasteur pipettes under the influence of capillarity and gravity, the pipettes being changed at two-minute intervals or more quickly if the blood flow was great enough to justify it. Blood samples were weighed, decolourised, and mixed with scintillation fluid (NE 260, Nuclear Enterprises Ltd), and the activity of ^3H in the blood samples was assayed by liquid scintillation counting. At the end of the experiment the animal was killed and the eye enucleated. The number of vortex veins was counted, and the state of the vitreous was determined by examination of the bisected globe with an operating microscope.

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In control experiments the experimental method was similar to that used in the hyaluronidase experiments, except that the injection of intravitreal hyaluronidase was omitted. The results of control experiments in normal eyes have been previously reported.[1] In relation to the state of the vitreous as examined under the operating miscroscope, the fellow eye in animals in which intravitreal hyaluronidase had been injected in one eye was used as a control.

Results

As had previously been found in control experiments,[1] all eyes had four vortex veins. There was, however, a marked difference in the state of the vitreous in eyes receiving hyaluronidase as compared with normal rabbit eyes, the vitreous in the former being liquid and rapidly running out of the bisected globe, unlike the latter in which the vitreous retained its firm gel-like characteristics.

In our initial study of normal rabbits the parameter used to characterise the rate of appearance of the ^3H_2O in choroidal blood was the mean transit time, the average time taken for a molecule of ^3H_2O to be cleared from the eye. However, the value of this quantity depends on the duration of the experiment, and the use of this parameter is inappropriate where experiments of differing lengths must be compared. In the present study control experiments lasted 80 minutes and those on rabbits injected with hyaluronidase only 60 minutes.

The difficulty in making comparisons between these two groups of experiments was resolved by fitting an exponential decay to the decrease in ^3H concentration in the blood samples after the maximum value had been reached several minutes after the start of the experiment. Examples of fitted decays are shown in Figs. 1 and 2 by the dot-dash lines and it is evident that these do give a good description of the variation of the data over much of the experimental time. We therefore took the time constant, τ, for the fitted decay as the index of rapidity of clearance of ^3H. τ has no intrinsic dependence on the length of experiment; smaller values of τ correspond to a more rapid removal of tritiated water.

The values of τ obtained from the experiments on the rabbits treated with hyaluronidase are detailed in Table 1 together with values obtained from reanalysing the control experiments described previously.[1]

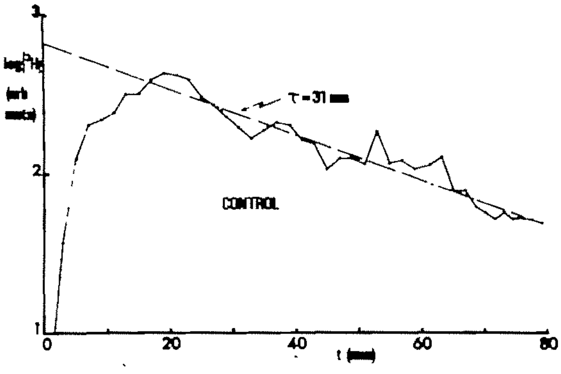

Fig. 1 *Example of exponential decay fitted to rate of decline of ^3H concentration in vortex vein blood samples after intravitreal injection of ^3H_2O in a normal rabbit eye.*

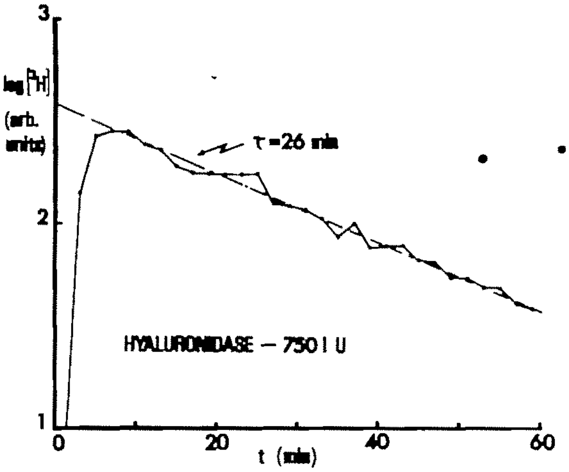

Fig. 2 *Application of an exponential decay to the decline in ^3H concentration in blood samples from a vortex vein after an intravitreal injection of ^3H_2O in an eye in which the vitreous hyaluronic acid had been depolymerised by the injection of hyaluronidase.*

Table 1 *Rate of movement of ^3H_2O from vitreous to choroid in normal rabbit eyes and in eyes injected with intravitreal hyaluronidase The rate of clearance of ^3H_2O from vitreous to choroid is increased in hyaluronidase treated eyes*

	Time constant (min)	
	Control eyes	*Hyaluronidase treated eyes*
	54	23
	24	12
	25	28
	26	26
	30	13
	31	18
	47	
	33	
	56	
Mean	36	20
SD	13	7
SE	4	3

0 01<P<0 02 (Mann-Whitney test)

Table 2 *Total recovery of ^3H_2O from one vortex vein after intravitreal injection of ^3H_2O in normal eyes and in eyes receiving an intravitreal injection of hyaluronidase*

	Amount of injectate recovered (per cent)	
	Control eyes	*Hyaluronidase treated eyes*
	18	30
	38	54
	23	14
	35	14
	27	13
	24	12
	26	
	24	
	13	
Mean	25	23
SD	8	17
SE	3	7

$0{\cdot}2<P<0{\cdot}5$ (Mann-Whitney test).

The mean time constant for the hyaluronidase series was 20±3 minutes (mean ± standard error) compared with 36±4 minutes for the control group. The difference between the two sets of time constants was tested by the non-parametric Mann-Whitney test and found to be significant at the 5% level ($0{\cdot}01<p<0{\cdot}02$; two-tailed).

The total recoveries of ^3H_2O are set out in Table 2 with the control data for comparison. A Mann-Whitney test showed no significant difference between the two groups of data, though the trend was for lower recoveries in the hyaluronidase series perhaps because of the shorter durations of experiments in this group.

Discussion

Although the results of the experiments on water movement from the vitreous to the choroid in normal control animals fitted the pattern expected for diffusional movement of water from vitreous to the choroid, we have not excluded the possibility of a pressure-dependent component of flow or indeed a movement dependent upon active transport in the pigment epithelium or resulting from the colloid osmotic pressure difference between the vitreous and the protein-rich extravascular spaces of the choroid.

The control animals used in these experiments were of the same strain, weight, and age as the animals receiving intravitreal hyaluronidase, and the experiment itself was similar in both groups of animals with the exception of the introduction of hyaluronidase into the eyes of the experimental group. In some respects it might have been better to have used the fellow eye of the same animal as a control, but this was precluded by the impossibility of achieving adequate access to vortex veins in each eye simultaneously. The question of leakage round the injection sites of either the tritiated water or the hyaluronidase had also to be considered. Experiments in which fluorescein was mixed with the injectate showed no evidence of leakage round the injection sites when the technique described was used, nor were significant differences found between the recovered amounts of injectate in control and experimental eyes (Table 2), which would have been expected had there been significant loss of injectate round the injection site in eyes receiving intravitreal hyaluronidase.

From the data presented here it does appear that vitreous hyaluronic acid can influence the diffusional movement of water in the vitreous. In the normal eye the polymerised hyaluronic acid is evidently a rate limiting factor, possibly one of several, in the processes of water transport from mid vitreous to choroid, since the rate of water transfer has been shown to be faster in eyes treated with hyaluronidase, and it is known that hyaluronidase depolymerises vitreous hyaluronic acid.[5,6]

It has long been accepted that the vitreous structure could act as a barrier to the passage through it of large protein molecules, cells, and the like, and indeed it has been shown that hyaluronic acid in various concentrations systematically reduces the diffusion of chemotactic peptides in solution[7] and also the movement of macrophages.[8] The question of the influence of hyaluronic acid on water movement has been less certain. Ogston and Sherman[9] showed that solutions of hyaluronic acid stabilised on micropore filters could slow down water flow, but Balazs (personal communication) has refuted the suggestion that hyaluronic acid in the vitreous would influence diffusional movement of water. On clinical grounds it has been suggested that intact vitreous gel may be capable of blocking open retinal holes, in some cases preventing retinal detachment.[10] It has also been postulated that vitreous tamponade of retinal holes in volume-reducing operations for retinal detachment may be important in relation to surgical cure of such detachments.[11] In particular it has been suggested that vitreous tamponade of a retinal hole might explain the flattening of the retina which commonly occurs after episcleral plombage where the retinal hole is not in contact with the indentation in the immediate postoperative period.[12]

The present study lends support to the view that intact cortical vitreous gel can limit the movement of water molecules, confirming that vitreous tamponade of retinal holes is a physical possibility.

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Colour vision of diabetics

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SUMMARY The Farnsworth-Munsell 100-hue test has been assessed as a screening test for the detection of diabetic retinopathy likely to benefit from laser photocoagulation therapy. Two hundred and thirty-two diabetic eyes of 126 patients were tested. The results were assessed both for total error score relative to age and for the presence of polarity. Although the incidence of abnormal colour discrimination was found to correlate with the severity of retinopathy, the test was not sufficiently selective to be of value as a screening test in the detection of retinopathy requiring treatment.

Diabetes is a common cause of blindness in the UK. The survey by Sorsby[1] showed it to be the fifth commonest cause of blindness in England and Wales, while in a recent study[2] confined to the west of Scotland diabetes ranked as the fourth commonest cause.

Treatment by photocoagulation is now widely available for patients with the more serious ocular complications of the disease, particularly exudative maculopathy and proliferative retinopathy. Some 1% of the population have diagnosed diabetes, while about 10% of diabetics develop retinopathy which threatens sight.[3] Such retinopathy, particularly of the proliferative variety, may be asymptomatic for a considerable time, yet early detection and timely laser photocoagulation can prevent progression to blindness.[4]

An effective screening test for the early detection of those diabetics with sight-threatening retinopathy would be of considerable value. Lakowski, Aspinall, and Kinnear[5] found that diabetic patients whose colour vision was assessed with the Farnsworth-Munsell 100-hue test[6] had higher error scores than did normal observers of similar ages. If retinopathy was present, the error score was further increased.

We have assessed the Farnsworth-Munsell 100-hue test in relation to its ability to separate diabetics with sight-threatening retinopathy from those with milder ocular disease.

Materials and methods

The Farnsworth-Munsell 100-hue test was performed by patients attending a diabetic medical clinic for routine ocular screening. The fundi of these patients were graded into one of four groups after ophthalmoscopic examination by an ophthalmologist. In addition a group of normal people, drawn from the staff of the department, were tested. No one with a known condition likely to impair colour discrimination was included in this group.

The groups examined were as follows: *Group N*—Normal persons. *Group NR*—Diabetics who showed no diabetic retinopathy on ophthalmoscopy. *Group B*—Background retinopathy. Those with opthalmoscopically visible retinal haemorrhages, hard exudates and microaneurysms with retention of good vision; patients with soft exudates (cotton wool spots) were excluded. *Group P*—Proliferative retinopathy; those with abnormal new vessels in the retina. *Group E*—Exudative maculopathy; those with macular or paramacular hard exudates and/or macular oedema and visual acuity below 6/18.

The test was performed under Illuminant C lighting conditions at an illumination level of approximately 200 lux in a VeriVide lighting cabinet (Leslie Hubble Ltd), and no limit was placed on the time taken. The test was performed monocularly and any appropriate near correction was used by the subject. The colour caps were presented to the observers in four sets of 21 or 22 caps as described by Farnsworth.[6]

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Table 1 *Numbers of 100-hue test results analysed by two methods of assessment for various categories of diabetic retinopathy. Both assessments include two subjects, one with one eye in group NR and the other in group B, and the second with one eye in group B and one in group E. The totals take account of these cases*

	Total error score assessment		*Polarity assessment*	
	Eyes	*Subjects*	*Eyes*	*Subjects*
Group N, normals	18	16	18	16
Group NR, no retinopathy	115	59	115	59
Group B, background retinopathy	55	31	28	15
Group P, proliferative retinopathy	42	24	13	8
Group E, exudative maculopathy	20	12	5	3
All diabetics	232	124	161	83
All subjects	250	140	179	99

Table 2 *Numbers of abnormally high 100-hue test total error scores in normal subjects and in patients with various grades of diabetic retinopathy*

	Eyes	*Subjects**
Group N, normals	3 (17%)	3 (19%)
Group NR, no retinopathy	28 (24%)	19 (32%)
Group B, background retinopathy	18 (33%)	11 (35%)
Group P, proliferative retinopathy	21 (50%)	14 (58%)
Group E, exudative maculopathy	19 (95%)	12 (100%)

*Abnormal score for one or both eyes.

In most cases the scoring was calculated by an automatic electronic system (OE 8500A F-M Hue Tester, Osprey Electronics) and in the remainder by the testing optician. With both methods the error for each colour cap was calculated and plotted according to the method of Farnsworth,[6] and the total error score for all 85 caps was computed. Two hundred and fifty eyes in 140 subjects were tested. The numbers tested in the various groups are shown in Table 1.

Total error scores were judged abnormal if they fell outside the 95th percentile for age as published by Verriest *et al.*[7] for monocular testing without previous binocular experience, and normal otherwise.

The 100-hue test score charts were also analysed to determine whether any showed a polarity of error score, that is to say whether there were two regions of higher error scores lying roughly diametrically opposite on the circular score chart. In an attempt to remove subjectivity from the identification of any such cases, a mathematical method based on the use of Fourier series was developed and applied to the test data. Full details of the mathematical method are given elsewhere.[8]

In essence, from the 85 individual cap error scores on the chart computer calculations generate a figure which is a measure of how marked is any polarity and indicate the axis of confusion. The detection threshold for polar distributions was similar for the computer method and for an experienced 100-hue test assessor. The test results for 179 eyes in 99 subjects were analysed for the presence of a polarity by the computer-aided method (Table 1).

Results

Abnormaly high errors were found for a significant number of diabetic patients whatever the grade of retinopathy present. No significant differences were found between the proportions of males and females with abnormal error scores in the various retinopathy classes, and accordingly the results presented here are not separated by sex.

The results are summarised in Table 2, where it will be seen that the proportion of abnormally high scores rose from 17% in normal eyes to 95% in the case of eyes with exudative maculopathy. 32% of diabetic patients without retinopathy showed an abnormal test result in one or both eyes, while 58% of those with proliferative retinopathy did so. From these results it is clear that many diabetics have abnormal colour discrimination and that colour vision generally deteriorates as the retinopathy becomes more severe. The results are shown graphically in Fig. 1.

The total error scores are further analysed in Table 3, where the effectiveness of using an abnormally high total error score as an indicator of the presence of serious retinopathy—either proliferative retinopathy or exudative maculopathy— is explored. From the table it can be seen that when used in this way the sensitivity of the test (the proportion of serious retinopathies detected) was 65% (40 out of 62 eyes). The specificity (the proportion of non-serious retinopathy showing normal colour vision) was 73%. If the data are examined on the basis of patients, the sensitivity and specificity become 72% and 66% respectively.

It was found that only 10 of the 179 100-hue test charts examined showed a detectable polarity. The 10 positive findings were composed of six eyes from five subjects with no retinopathy and four eyes of four subjects from the proliferative group. The evidence is insufficient to say whether the incidence of polarity

Table 3 *Analysis of total error score data for serious diabetic retinopathy (groups P and E combined) and non-serious retinopathy (groups NR and B combined) Figures are for numbers of eyes.*

	Serious	*Non-serious*	*Totals*
Abnormal score	40	46	86
Normal score	22	124	146
Totals	62	170	232

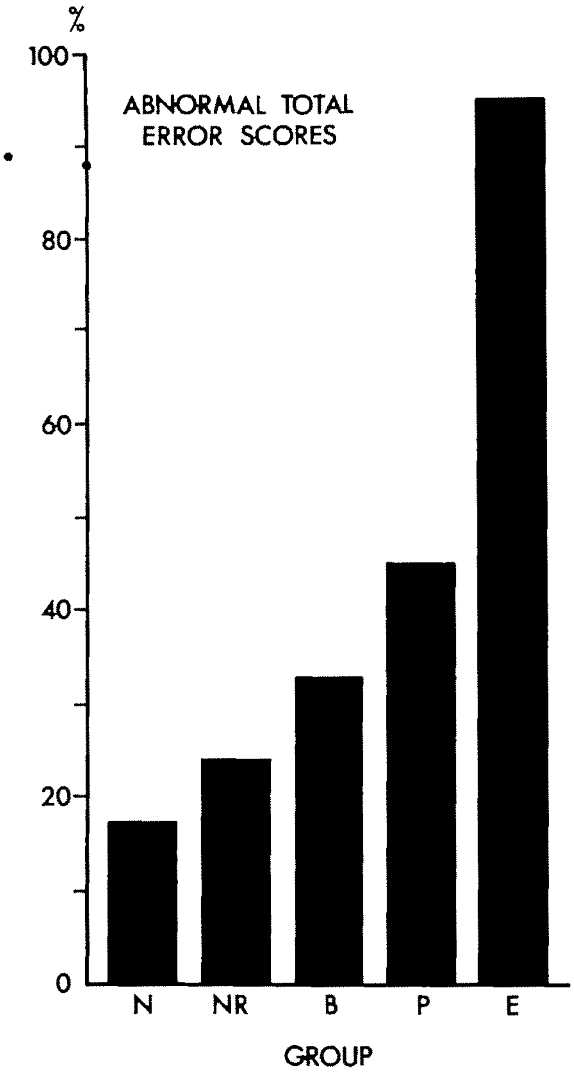

Fig. 1 *Percentages of eyes returning abnormally high total error scores for the 100-hue test. Subject categories: N—normals, NR—no retinopathy, B—background retinopathy, P—proliferative retinopathy, E—exudative maculopathy.*

varied in any systematic way with the grade of retinopathy.

Where a polarity was detected there was no ambiguity in the axis of colour confusion. For eight eyes of eight subjects, four each from the no retinopathy and proliferative groups, the axis of confusion ran between caps 81 and 7 and was therefore a blue-yellow axis, while the remaining two charts, for the two eyes of a 74-year-old man with no retinopathy, showed red-green axes running through caps 27 and 29.

Discussion

It is well established that colour vision is affected by diabetic retinopathy. Colour vision is a function of the cones, and patients with exudative maculopathy would be expected to demonstrate the most marked defects of colour vision. Our results confirm this; 95% of eyes (100% of subjects) with exudative maculopathy had an abnormally high total error score for their age.

In some cases of proliferative retinopathy areas of capillary closure may be situated peripherally in the retina where they might be expected not to influence colour vision, while in other patients intraretinal microvascular abnormalities or capillary closure may affect the macular circulation and lead to a deterioration of colour vision. In our proliferative retinopathy group 50% of eyes (58% of subjects) had significantly defective colour vision.

In addition to these more or less expected observations we also found significant defects of colour vision in many diabetics with no clinically visible retinopathy or only simple background retinopathy. In these two categories 24% and 32% of eyes (32% and 35% of subjects) respectively showed abnormally high error scores. The mechanism of this deterioration of colour discrimination remains obscure, but it may result from early damage to the cones or their neuronal connections, which cannot be detected ophthalmoscopically, as previously suggested by Kinnear.[9]

Our primary aim was to determine whether the 100-hue test might be of value in separating those patients with retinopathy requiring treatment from those who did not. It is clear from the results presented in Table 3 that the test does not provide an effective means of doing this. About 35% of those with serious retinopathy are not detected by the criterion of the total error score; this figure is too high for the test to be considered an effective screening method.

A study of the contrast sensitivity performance of diabetics produced a rather similar result.[10] Although diabetics as a group displayed a significant reduction in contrast sensitivity as measured by the Arden grating test, the changes were not sufficiently large in relation to the normal range for effective identification of individual diabetics with retinopathy on the evidence of the test result alone.

Of the 161 diabetic eyes examined for polarity only 10 had a significant polarity. The red-green polarity found in the results of a 74-year-old man may well have been a congenital colour vision defect, leaving only eight positive results to be attributed to diabetic retinopathy. Colour vision testing with the Pickford-Nicholson anomaloscope[3] has shown that diabetics have an increased incidence of poor blue-yellow discrimination. It may be that our investigations have not shown this to any extent because, as suggested by Taylor,[11] the divisions between the four boxes of colour caps in the 100-hue test fall at disadvantageous points of the colour sequence for the demonstration of these particular defects.

CONCLUSIONS

The Farnsworth-Munsell 100-hue test demonstrates deteriorating colour discrimination with increasing severity of diabetic retinopathy. The test is not on its own sufficiently specific to be of value as a screening test for the identification of serious diabetic retinopathy requiring laser treatment.

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Type IV melanosomes of the human albino iris

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SUMMARY Electron microscopy of an iris biopsy specimen from a clinically tyrosinase-negative human albino demonstrated type IV mature melanosomes. Possible mechanisms for the formation in this condition of these organelles, which have not previously been described at this site, are discussed.

Melanosomes, the pigment-bearing organelles of melanocytes, have been classified into four categories.[1 2] The first two categories, types I and II, represent the premelanosomes, which are shuttle-shaped organelles formed in the endoplasmic reticulum, and types III and IV, in which there is progressive obliteration of the shuttle-shaped organelles into homogeneous, spherical, membrane-bound organelles filled with melanin. This is thought to be due to catalysis of tyrosine into dopamine by tryosinase. Albinos of the tyrosinase-negative oculocutaneous type (TNOCA)[3] were thought not to have organelles of the mature type IV variety on previous studies of the skin, hair bulb, and eyes.[4]

In the normal eye three types of melanin-containing cells are seen in the iris: the stromal melanocyte, derived from neural crest; the pigment epithelial cell, of neuroectodermal origin; and the phagocytic clump cell of Koganei.[5] A previous light microscopic study of the eyes of a TNOCA patient[6] failed to show iris stromal melanocytes; the authors did not examine pigmented epithelial cells of the iris by electron microscopy. In our case all three types of iris melanin-containing cells were seen, a finding which has not previously been reported.

Patients, materials, and methods

An iris biopsy was performed during routine cataract surgery and intraocular lens implantation on the right eye of a 62-year-old woman who was clinically a classical case of TNOCA.

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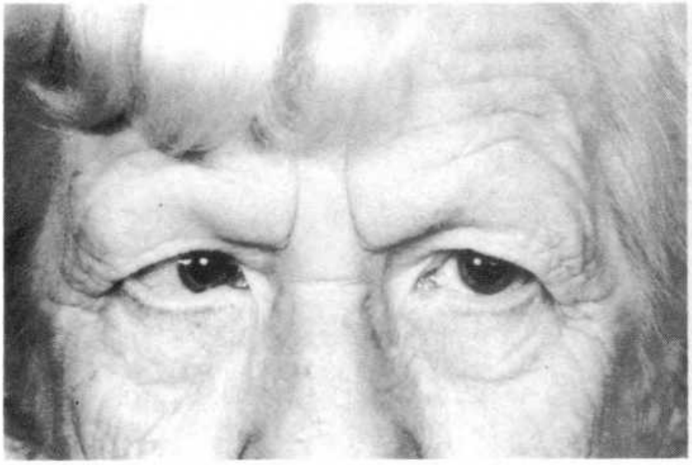

Fig. 1A

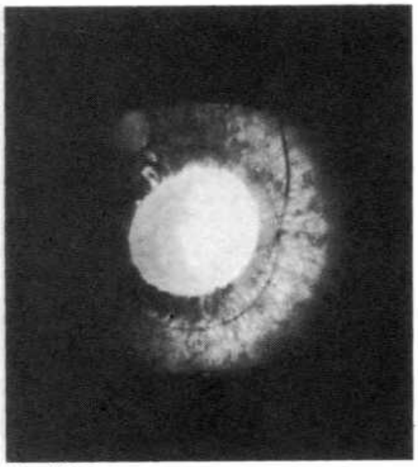

Fig. 1B

Fig. 1A *Face of the patient. Notice white hair, eyelashes, and eyebrows, and a right convergent squint.*
Fig. 1B *Postoperative photograph of the right iris shows gross transillumination against the red reflex. The peripheral iridectomy can be seen superiorly and a Sinsky intraocular lens implant is seen outlined against the red reflex.*

She had had white hair all her life with a pale skin and no freckles or naevi. Her irides were pale grey with marked transillumination (Fig. 1). She was mildly photophobic, with congenital nystagmus, a convergent squint, and visual acuities of counting fingers in the right eye and 6/60 in the left eye. She had a senile cataract in the right eye and typical albinoid fundi. The iris tissue taken from the peripheral iridectomy at surgery was placed in cold Karnovsky (buffered glutaraldehyde and paraformaldehyde) fixative and allowed to reach room temperature. The biopsy specimen was processed and examined in an electron microscope. The melanocytes were photographed and the cell areas and the numbers and areas of melanosomes measured by means of computerised image analysis.

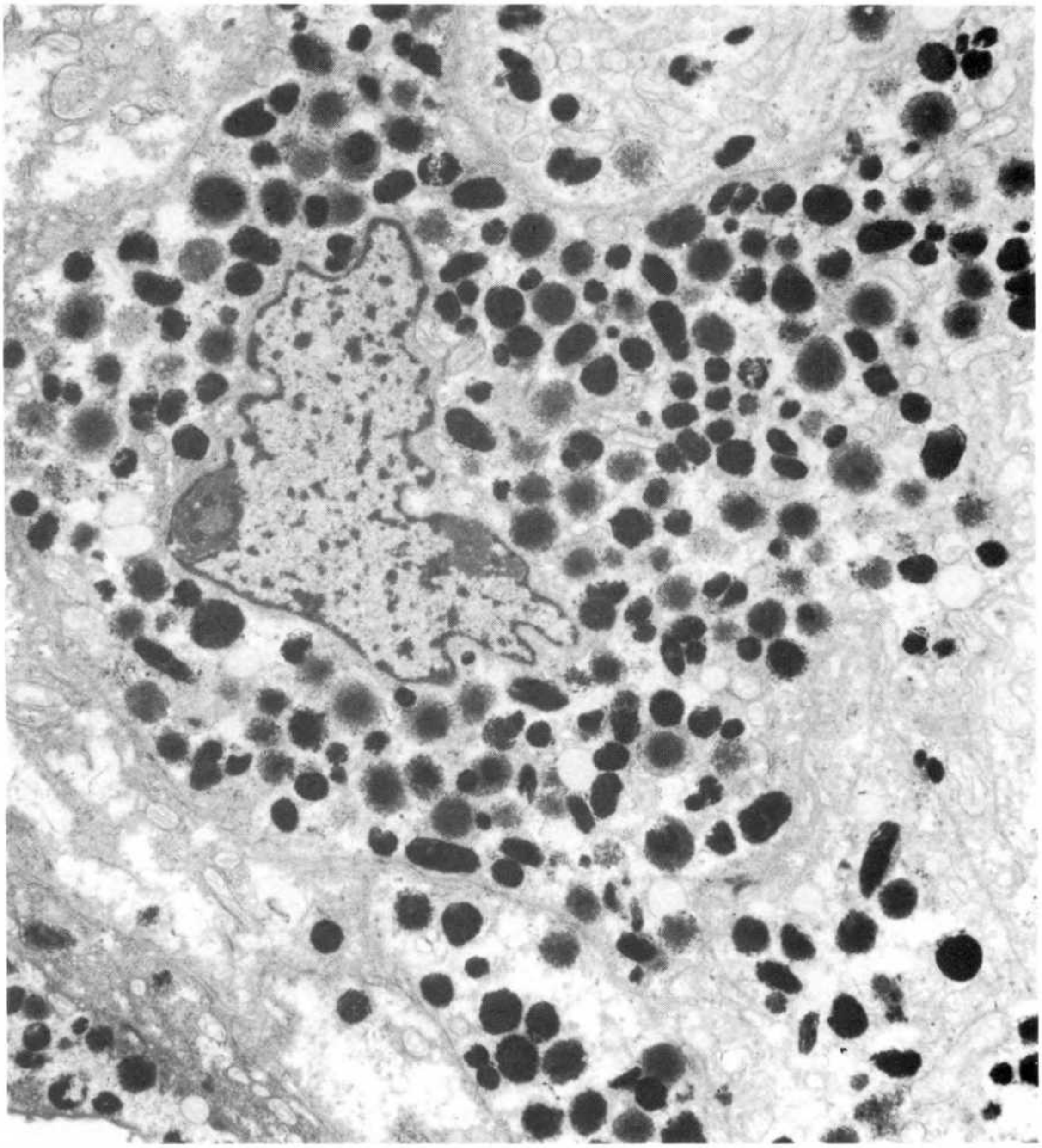

Fig. 2 *Pigment epithelial cells of TNOCA iris containing large numbers of type IV and III mature melanosomes. (×20 000).*

Results

All three type of melanin-containing cells could easily be identified in this biopsy. There were stromal melanocytes containing small but normally formed mature melanosomes of the type IV variety as well as premelansomes. There was also a layer of pigment epithelial cells containing larger melanosomes of all types, including types III and IV (Figs. 2 and 3). Phagocytic clump cells of Koganei were identified by the presence of larger groups of melanotic particles, not individually membrane bound, contained within lysosomal structures containing large lipid droplets (Fig. 4).

The high statistical significances reached in the following data and tests must be viewed in the light that only a single case was available for study.

The number of stromal melanocytes in the albino patient was not significantly reduced when compared with those in the control population, 54 cells in 6 grid squares compared with a mean of 69 cells in 9 grid squares in the controls. The area of the melanocyte cytoplasm was also not significantly smaller, though very large cells were not seen in the albino and were in the controls. The mean melanocyte cytoplasmic area of the controls was 61 μm^2 (SE 18 μm^2) compared with 19·86 μm^2 in the albino patient, but many of the control melanocytes were also small, one

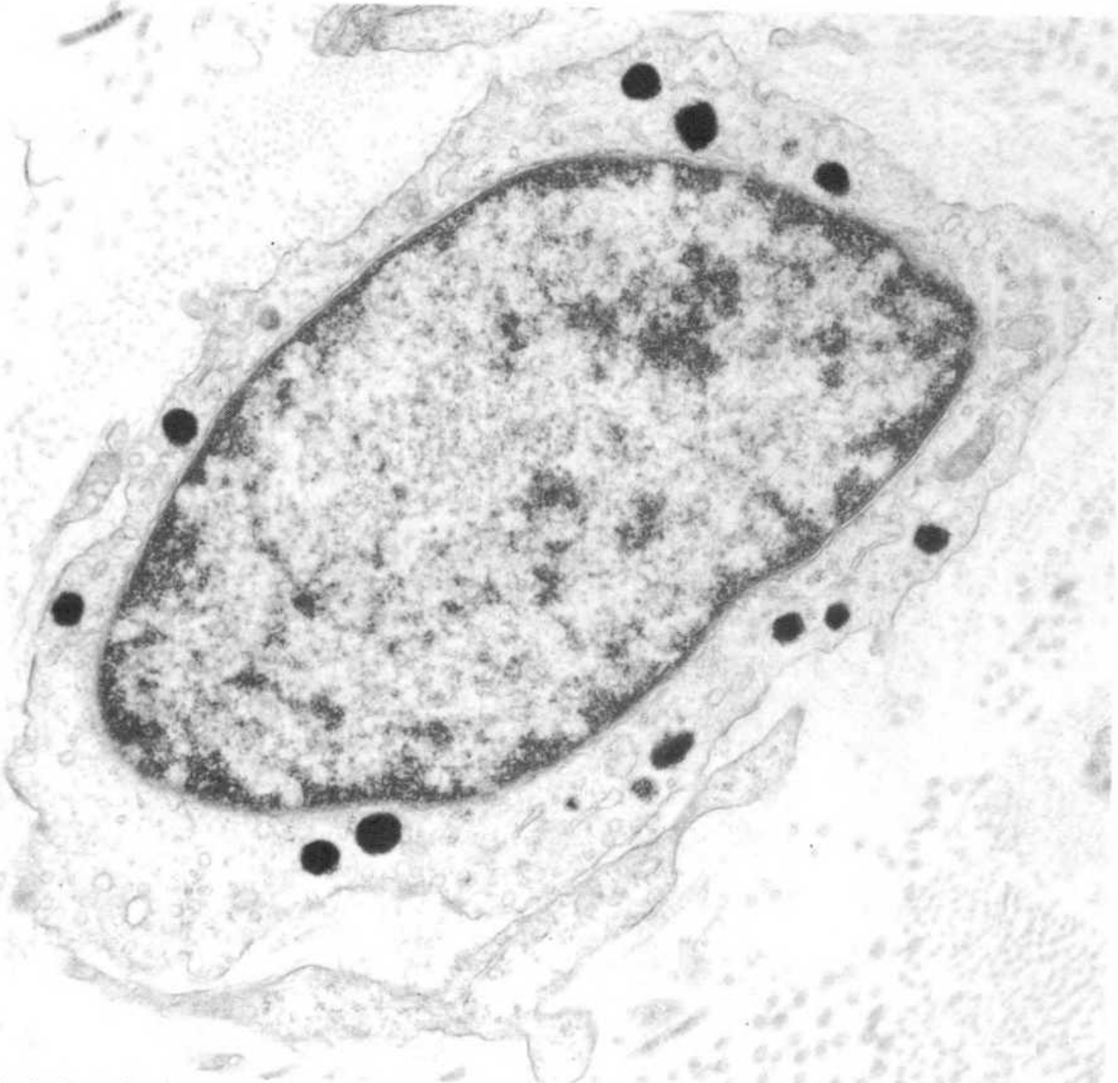

Fig. 3 *Stromal melanocytes in TNOCA iris containing mature type IV membrane bound melanosomes.* (×20 000).

control having a mean melanocyte cytoplasmic area of 27 μm^2 (this patient had blue eyes).

The number of melanosomes within control stromal melanocytes was not significantly greater (53·77, SE 11·2) than in the albino (23·3, SE 5·76).

However, there were markedly more type II melanosomes within the albino stromal melanocytes, where 19% were type II, 61% type III, and only 20% type IV, whereas the controls had <1% type II (premelanosomes), 29% type III, and 70% type IV. 10% of pigment epithelial melanosomes were type II compared with less than 2% in controls.

Type II melanosomes were difficult to see in control patients. When melanosomal areas were calculated, only type III and type IV melanosomes were measured in the albino. Measurements were made of 3305 control stromal melanosomes and 291 albino type III and IV melanosomes. The mean stromal melanosomal area was significantly reduced in the albino (0·0263 μm^2, SD 0·0101) compared with the controls (0·0438, SD 0·0061) ($p<0{\cdot}001$).

A similar significant difference was seen in the size of the type III and IV melanosomes of the pigment epithelial melanocytes. 1522 control pigment epithelial melanocytes were measured and compared with 269 type III and type IV melanosomes in the pigment epithelial cells of the albino. The mean area of the control patients' melanosomes was 0·397 μm^2 (SD 0·059) compared with 0·141 μm^2 (SD 0·066) in the albino ($p<0{\cdot}001$).

Discussion

The presence of mature forms of melansomes especially in stromal cells in this biopsy specimen came as a surprise, even though Fitzpatrick and Queredo[2] had predicted that they might occur. Fulton *et al.*[6] showed retinal pigment epithelial melanosomes and desc-

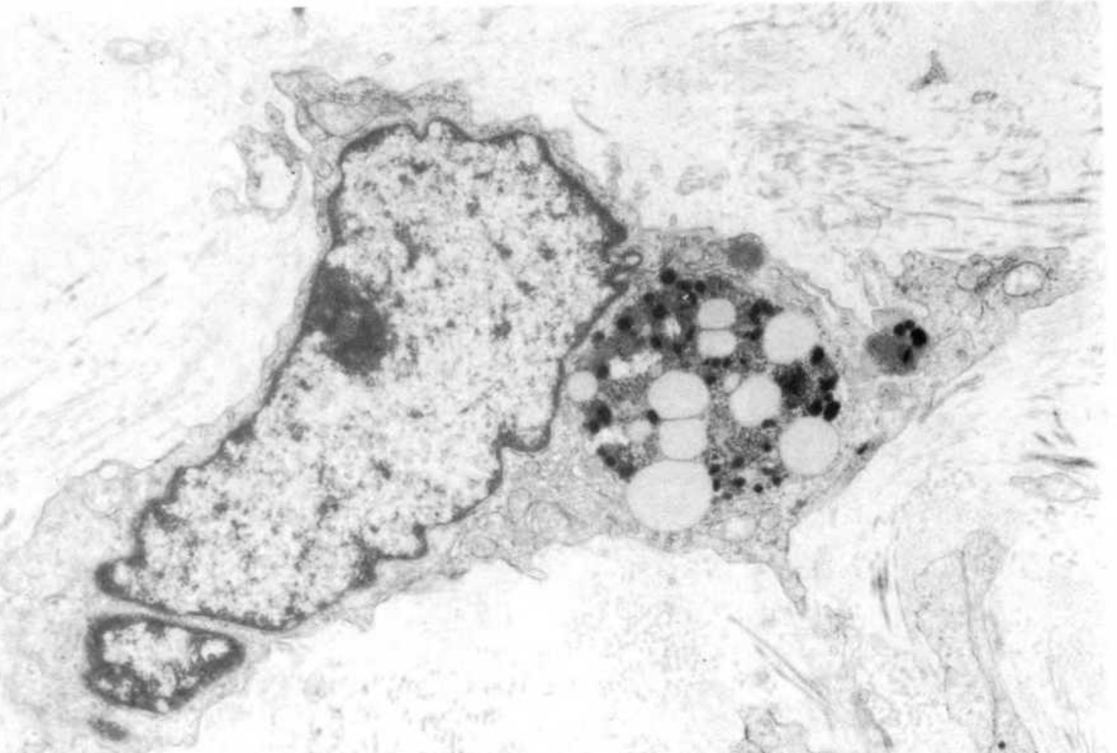

Fig. 4 *Phagocytic clump cell of Koganei containing melanin fragments within lysosome with lipid droplets.* (×*13 500*).

ribed the iris epithelium as pigmented, but they failed to show the stromal melanocyte at light microscopic level, and it had not been anticipated that they could be easily seen at electron microscopy. Animal studies may have been misleading, since animals do not have the greyish irises seen in human albinos, even of the TNOCA variety. The marked transillumination of the albino patient's iris (Fig. 1B) arises presumably both as a result of increasing numbers of premelanosomes, compared with controls, and the smaller size of the type III and IV melanosomes in melanocytes of both stroma and pigment epithelium.

From this biopsy specimen it appears that melanin can be laid down in organelles normally, in the presumed absence of the catalyst tyrosinase, though fewer melanosomes are fully pigmented. Although a recent paper[7] has suggested that a negative hair bulb or tyrosinase assay in TNOCA may be a result of insensitive assays or the presence of inhibitors, and has described tanning in a patient with TNOCA, it is possible that melanin formation can occur in the absence of the specific enzyme tyrosinase by two alternative pathways. One way is to use another enzyme catalyst such as endogenous peroxidase found in many cells, including mast cells,[8] which are also present in the iris stroma.[9] These enzymes can act independently of tyrosinase and have been shown to be present histochemically at many sites. An alternative and simpler mechanism can also be postulated.

If tyrosinase is acting as a catalyst, then theoretically the conversion of tyrosine to dopamine should occur slowly by itself in the absence of the catalyst. The slowness of this reaction may explain why no mature melanin was seen within the iris stromal cells of the albino child previously described,[4] who was only 13, whereas our patient was 62. The formation of the phagocytic clump cells of Koganei implies that the melanin-containing cells are also being broken down over a period of time.

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Enterobacter cloacae ulceration in a failed corneal graft: a case report

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SUMMARY A 70-year-old female developed a bacterial ulcer in a previously rejected corneal graft. Cultures identified the pathogen as *Enterobacter cloacae*. Intensive topical antibiotic therapy arrested the progress of the ulcer, and the epithelial defect healed in one week; there was no resultant stromal thinning. Factors which may have predisposed the cornea to ulceration by this organism of relatively low virulence include chronic oedema following graft rejection, topical corticosteroid therapy, and tear insufficiency.

Bacterial corneal ulcers pose a serious threat to the eye. Bacterial keratitis may be caused by both Gram-positive and Gram-negative organisms. Gram-positive organisms most commonly causing keratitis include *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Str. viridans*. Gram-negative corneal ulcers are most frequently caused by *Pseudomonas aeruginosa*, *Moraxella lacunata*, and *Serratia marcescens*.[1] Occasionally genera of the family Enterobacteriaceae such as *Klebsiella* cause corneal ulceration.[2] A case of corneal ulceration due to *Enterobacter cloacae*, the first published report, is presented to underscore the importance of this unusual ocular pathogen.

Case report

A 70-year-old female with anterior cortical cataracts underwent extracapsular cataract extraction and anterior chamber intraocular lens implantation of the left eye in January 1977. The eye subsequently developed posterior capsule opacification and cystoid macular oedema In 1978 she was referred for treatment of pseudophakic bullous keratopathy Visual acuity in the left eye was light perception. Her entire cornea was oedematous with epithelial bullae and stromal oedema, with folds. The endothelium was not visible. An Optical Radiation Corporation anterior chamber intraocular lens implant was in place. Behind the lens was a dense membrane adherent to the edge of the pupil with a white horizontal band through the visual axis. Corneal sensation was markedly decreased. Schirmer testing with anaesthesia was 8 mm and 4 mm, OD and OS respectively. She underwent penetrating keratoplasty with an 8·5×8·0 mm graft, pars plana vitrectomy, and excision of the pupillary membrane in September 1978.

Five years later she developed an acute endothelial graft rejection, which was treated by topical steroid therapy. The inflammatory episode subsided, but the graft remained oedematous, with epithelial microbullous changes, mild punctate staining, and persistent stromal oedema. She continued to use fluorometholone drops four times daily.

In January 1984 she reported a three-day bout of epiphora, foreign body sensation, and swelling of the left eyelid. On examination visual acuity of the left eye was hand motions at 6 inches (15 cm). There was slight erythema of the left upper lid with mild swelling. The cornea had microbullous epithelial changes and a 3·0×1·2 mm epithelial defect with an underlying dense, white stromal infiltrate which was paracentrally located in the oedematous corneal transplant. A small hypopyon was present inferiorly (Fig. 1).

The patient was admitted to the WK Kellogg Eye Center and treated intensively with topical bacitracin (10 000 units/ml) and fortified gentamicin (13·6 mg/ml) drops to alternate every 15 minutes around the clock. The FML drops were tapered and discontinued over a three-day period.

Gram stain revealed Gram-negative bacilli. Cultures showed *Enterobacter cloacae*, verified by

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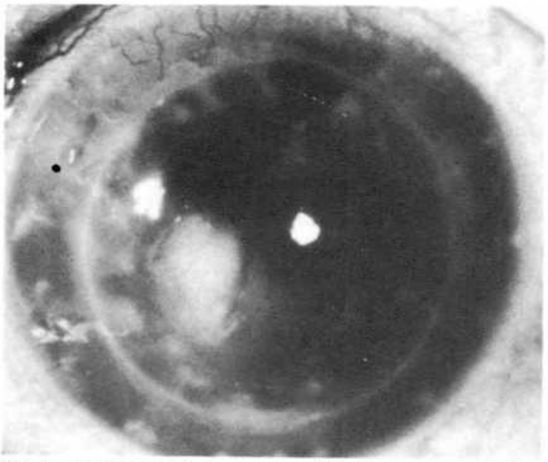

Fig. 1 *Pretreatment appearance of* E. cloacae *corneal ulcer is shown.*

the Analytical Profile Index system. The organism was sensitive to gentamicin, tobramicin, and sulphacetamide; it was resistant to bacitracin.

On treatment day 2, when cultures revealed *Enterobacter cloacae*, sulphacetamide 15% drops were substituted for bacitracin. On the fourth treatment day the infiltrate was diminished, and the frequency of drop instillation was tapered. On treatment day 7 the epithelial defect had healed. At the time of discharge from the hospital the corneal epithelium was intact and the stroma was minimally scarred. There was residual oedema secondary to previous graft rejection. There was no significant stromal thinning.

Discussion

Corneal ulceration solely due to *Enterobacter cloacae* has not been previously reported in the literature. One case of endophthalmitis ascribed to this organism was noted by Rose and Koch in 1966.[3] *Enterobacter cloacae* and *Actinobacter calcoaceticus* have been isolated in several cases of acute polymicrobial conjunctivitis.[4] Recently Boisjoly *et al.* reported a case of corneal superinfection by this organism in a patient with recurrent herpes simplex keratitis.[5]

Until the mid 1960s *Enterobacter cloacae* was not considered to be an important pathogen anywhere in the body. It was thought to be an organism which primarily colonised the gastrointestinal tract but was not responsible for disease. Recently clinicians have begun to recognise its virulence. John *et al.* noted that *Enterobacter cloacae* was present in 4–12% of all cases of Gram-negative bacteraemia.[6] It has also been implicated in endocarditis, meningitis, septic arthritis, urinary tract infection, pneumonia, and pelvic inflammatory disease.[6]

The importance of host defences has been widely recognised, and organisms previously considered to be non-pathogenic have become important vectors of disease in patients whose immune systems are compromised. In John and colleagues' series burn patients were cited as being at high risk for developing *Enterobacter cloacae* bacteraemia.[6]

In the eye the corneal epithelium is recognised as an important barrier against infectious keratitis. Besides providing a physical barrier to the entry of bacteria into the stroma[7] intact epithelium may actively phagocytise bacteria in response to chemotactic stimuli.[8] Tears also protect the eye by mechanically washing away micro-organisms. Tear film IgA facilitates opsonisation and may also inhibit adherence of bacteria to ocular mucosa. Other components of tears, such as lysozyme, are bactericidal.[9,10]

Impairment of normal ocular defences may leave the eye more vulnerable to attack by pathogens. For example, studies have shown that persistent defects in the corneal epithelium increase the risk of corneal ulceration and perforation.[11] Concomitant topical steroid therapy may also exacerbate ulceration.[12,13]

The patient presented in this report may have been particularly at risk for corneal ulceration by *Enterobacter cloacae* because of impairment of local host defences. The corneal epithelial barrier had been disrupted by chronic oedema following a previous episode of graft rejection, decreased tear production, and long-term topical corticosteroid therapy. It is likely that the patient directly introduced this stool-based organism into the eye by means of poor toilet hygiene and inadequate hand washing.

Fortunately the infection was controlled by topical sulphacetamide and gentamicin drops. *Enterobacter cloacae* is usually resistant to ampicillin and can produce a cephalosporinase which may deactivate some cephalosporins.[14] Aminoglycosides have been the most effective drugs against the organism and sepsis has been treated with carbenicillin and an aminoglycoside.[15] However, there have not been any organised clinical trials to delineate the most efficacious regimen for treatment of systemic or ocular infections caused by *Enterobacter cloacae*.

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Progressive hemifacial atrophy: a case report

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SUMMARY A case of a 28-year-old Caucasian female with progressive hemifacial atrophy and atrophy of the rhomboid muscles on the ipsilateral side is reported. The literature on this condition and its treatment is reviewed.

The first published reports on progressive hemifacial atrophy were attributed to Parry[1] in 1825 and Romberg[2] in 1846. Characterised by progressive atrophy of the skin, subcutaneous tissue, muscle, cartilage, or bone, the condition can leave a marked deformity on one side of the face. Extension to the ipsilateral upper extremity and to the entire half of the body have also been described. The condition usually presents during the first two decades of life, often beginning in the paramedian area of the face. It may cease at any stage and leave only a minimal disfigurement.

Progressive hemifacial atrophy should be distinguished from localised scleroderma, hemifacial microsomia, traumatic fat necrosis, atrophy secondary to facial paralysis, and unilateral patrial lipodystrophy. There has been speculation on the relationship between hemifacial atrophy and localised scleroderma. Wartenberg[3] in his extensive review concluded that the two conditions are essentially the same, and this view has been supported by Rees.[4] However, Crickler *et al.*[5] and Dawson[6] concluded that scleroderma is a different entity.

Case report

In April 1982 a 28-year-old Caucasian female patient with a history of progressive enophthalmos on the right side was referred to a consultant ophthalmologist by her general practitioner. Photographs of the patient taken in the past show the enophthalmos to be of gradual onset, though the patient was more aware of the change during the previous 12 months. A lipoma was removed from the patient's scapula region 10 years previously, but otherwise the medical, surgical, and family history were uneventful.

On examination facial asymmetry was obvious, with noticeable enophthalmos on the right side, but function of the extraocular muscles was unaffected. Some atrophy of the right facial musculature was obvious, particularly over the zygomatic bone and the region of the upper lip (Fig. 1). Extensive radiological investigation of the skull and facial bones revealed no significant abnormality apart from the right ramus of the mandible which was found to be diminished both in height and width with impaction of the right mandibular wisdom tooth. From the above findings a diagnosis of progressive hemifacial atrophy was arrived at.

General examination also revealed a degree of atrophy of the rhomboid muscle on the same side, as a consequence of which the vertebral border of the scapula was thrown into prominence (Fig. 2).

A chest *x*-ray showed prominent hilar shadows, and as the erythrocyte sedimentation rate (ESR) was slightly raised at 23 mm in the first hour the possibility of pulmonary sarcoidosis was suggested. Further investigations undertaken by a consultant physician, including the Kveim test and serum angiotensin converting enzyme level, failed to support this, and tuberculosis was also excluded. Electromyographic and nerve conduction studies on the atrophied rhomboid muscles indicated no evidence of denervation.

The patient was subsequently referred for both plastic and maxillofacial surgical opinions. The consensus of opinion after extensive consultation and discussion was that her facial appearance was acceptable and she should be kept under periodic review. However, excision of the impacted right mandibular wisdom tooth was necessary, and this was carried out for her uneventfully under general anaesthetic.

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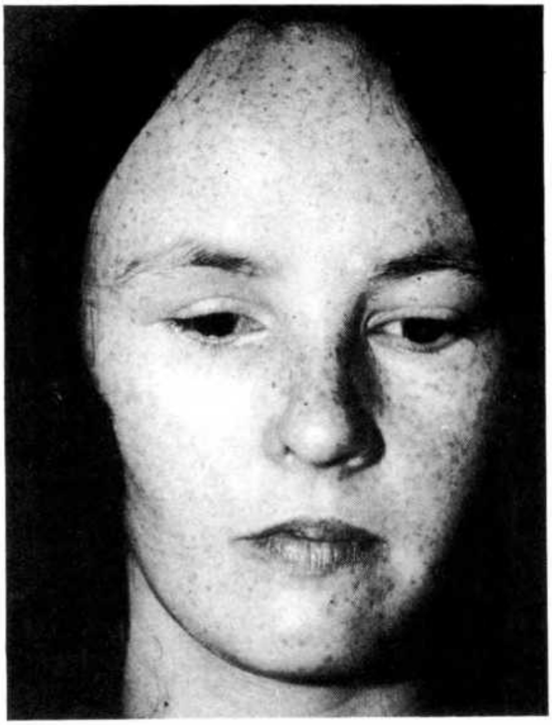

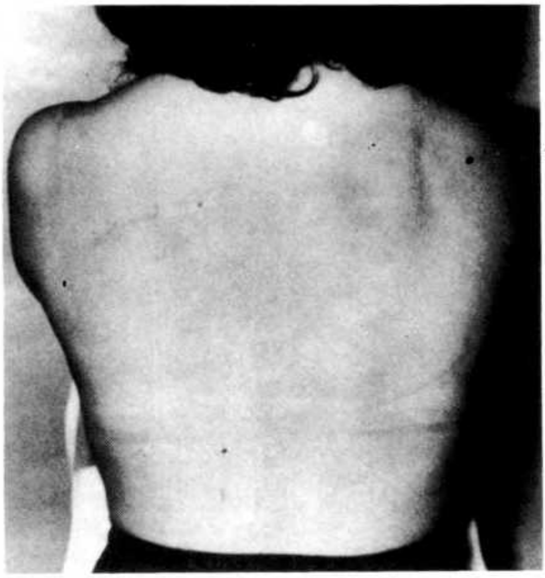

Fig. 1 *Front view of the face.*

Fig. 2 *View of upper back showing some atrophy over the region of rhomboid muscles on the patient's right side.*

Review of the patient in March 1984 showed no significant change in her condition.

Discussion

Trauma, infection, genetic factors, autoimmunity, and peripheral trigeminal neuritis have all been incriminated in the initiation of the process of progressive hemifacial atrophy. In one case[7] the attributed traumatic factor was extraction of a tooth. Wartenberg,[3] however, considered the primary local factor to be a disturbance of fat metabolism resulting from trophic malfunction of the cervical sympathetic system.

Aracena *et al.*[8] and Muchnick *et al.*[9] in an extensive ophthalmological review of hemifacial atrophy reported the most common ocular involvement to be enophthalmos due to atrophy of the orbital fat. Changes in the eyelids were also common, with varying degrees of eyelid atrophy, which in turn can lead to corneal changes such as keratitis and ulceration. Coloboma as an associated entity has also been reported,[10] as have optic neuritis and facial paralysis.[11]

Goldhammer *et al.*[12] reported a case of progressive hemifacial atrophy with extensive atrophy of the walls of the maxillary sinus but only minimal soft tissue involvement. Prolapse of the subcutaneous tissue and orbital fat into the maxillary sinus simulated the presence of a tumour and necessitated surgical exploration. Foster[13] reported the effect on dental development and stressed that, if the condition is present during the growth phase, it may result in reduced growth of the roots of the teeth on the affected side. Bramley and Forbes[14] reported an interesting case of progressive hemifacial atrophy presenting with spontaneous fracture of the atrophied mandible.

In the detailed reviews by Arachambault and Fromm[7] and Wartenberg[3] various extrafacial manifestations have been reported. They include atrophy of kidney, adrenal glands, ovary, and even the entire half of the body. Hickman and Shiels[15] reported a case of marked ipsilateral with contralateral lower extremity involvement. Migraine and epilepsy have also been observed, while Dawson[6] reported a case of pulmonary sarcoid in conjunction with hemifacial atrophy.

Treatment in progressive hemifacial atrophy is primarily directed towards augmentation of the affected areas for aesthetic reasons. Secondary procedures on uninvolved areas of the face may improve the result. The reconstructive procedure is determined by the particular phase of the disorder (active or 'burned out'), location, and the degree of the deformity to be corrected.

The use of autografts—for example silicone polymer, pedicled, and free flaps[16]—have all been described. Rees *et al.*[17] following a 10-year study on the use of injectable silicone fluid in hemifacial atrophy reported significantly good results. They further emphasised that the silicone fluid should be injected in small repeated doses followed by thoroughly massaging the area immediately afterwards to obtain the optimum results. Bart and Kopf[18] also reported good aesthetic results with this method.

The introduction of free tissue transfer by microvascular anastomosis opened a new era in reconstructive surgery. Harashina and Fujino[19] and Shintomi *et al.*[20] reported good results in hemifacial atrophy with the transfer of vascularised dermis flaps from the deltopectoral and groin regions to the facial region. Although it is widely held that surgery to correct facial hemiatrophy should be performed only after the progress of the disease has come to a halt, Converse[16] and Shintomi *et al.*[20] favoured operation at an early stage. They further believe that a free flap with a new independent source of blood which will constantly feed the affected tissue will have a beneficial influence on the disease process in addition to offering the greatest chance of success in the reconstruction of the deformity caused by this puzzling condition.

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Beauvaria bassiana keratitis

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SUMMARY The cornea of a 64-year-old white male underwent progressive thinning following removal of a foreign body and after treatment with topical antibiotics and corticosteroid. Initial attempts at laboratory identification of an infectious agent were negative. The process progressed to corneal perforation. After a penetrating keratoplaty, histopathological examination of host button tissue showed a fungus, identified as *Beauvaria bassiana* on culture.

The incidence of fungal keratitis has increased in recent years. The fungal genus *Beauvaria* is an insect pathogen found in the soil. Interestingly, it holds a rather prominent place in historical microbiology, as it was the first organism shown to produce a disease.[1] Only two cases of beauvaria infection in man have been reported.[2,3] Although Lichaa[4] and Langeron[5] reported a case of keratoconjunctivitis caused by beauvaria, Langeron later reclassified the fungus into a different genus.[6] In this report we present the first case of beauvaria keratitis.

Case report

A 64-year-old white male Massachusetts farmer was referred to the New England Medical Center Ophthalmology Service in November 1980. In June 1980 an asymptomatic 'spot' on his right eye was noted. In October 1980 he sustained a corneal abrasion in the right eye. A corneal foreign body described as 'vegetable matter' surrounded by a white stromal infiltrate was noted in addition to the abrasion. The foreign body was removed. Corneal scraping revealed 'polymorphonuclear leukocytes and no organisms' on Gram stain. Bacterial and fungal cultures had no growth. The patient was placed on gentamicin drops without a change in clinical appearance. He was then referred to the New England Medical Center's (NEMC) Corneal/External Disease Service. On initial examination there the patient complained of mild photophobia and had a foreign body sensation. Best corrected visual acuities were 6/12 in the right eye and 6/6 in the left eye. The conjunctiva of the right eye was 1+ diffusely injected. A white inferior paracentral infiltrate without thinning was present on the cornea of the right eye. The anterior chamber of the right eye was without flare or cells. The initial impression was of an inflammatory keratitis secondary to a previous foreign body. Gentamicin drops were discontinued. Chloramphenicol-polymyxin-hydrocortisone ointment was begun three times daily and the patient was returned to the referring ophthalmologist.

After initial improvement the infiltrate increased in size. Chloramphenicol-polymyxin-hydrocortisone was stopped and gentamicin drops were restarted. The patient's discomfort worsened, conjunctival injection increased, and the corneal infiltrate increased in size. The gentamicin drops were stopped after several days and dexamethasone ointment four times daily was begun. The patient was again referred to the New England Medical Center. He had only a mild foreign body sensation.

Visual acuity on that date (8 January 1981) was 6/10 in the right eye. The conjunctiva was normal. An infiltrate of approximately 4 mm was noted inferotemporal to the visual axis. The cornea was approximately 40% thinned at the superior aspect of the lesion. A dense stromal haze surrounded the region. The anterior chamber was normal. The stromal thinning was thought to be a secondary effect of the steroid, and an attempt to taper the drug was made. The patient returned one week later (15 January 1981), at which time no change was noted in his clinical appearance. Corneal scrapings for bacterial and fungal cultures were repeated. A corneal biopsy

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showed moderate stromal oedema and a few scattered neutrophils. Methanimine silver and Gram stains for fungi and bacteria were negative. Bacterial and fungal cultures were negative. The Patient was seen on 19 January 1981, at which time no change in the clinical picture could be detected. A soft contact lens was placed on the eye, and chloramphenicol-polymyxin-hydrocortisone ointment twice daily was reinstituted. The contact lens was removed by the referring ophthalmologist three days after insertion owing to 'iritis.' Atropine drops were added in addition to the chloramphenicol-polymyxin-hydrocortisone. The patient was seen by the referring ophthalmologist on 4 February 1981, when a corneal perforation was noted. He was referred back to New England Medical Center.

The perforation was initially sealed with isobutyl cyanoacrylate glue. The patient underwent a penetrating keratoplasty two days later. Histological sections of the cornea showed an infiltrate composed of necrotic debris, neutrophils, and mononuclear inflammatory cells at the perforation site. The adjacent stroma was oedematous and infiltrated by numerous acute and chronic inflammatory cells (Fig. 1). Occasional hyphae were seen in deep stroma and adjacent to Descemet's membrane. Cultures from the host button grew *Beauvaria bassiana*, a finding confirmed by both the Massachusetts and New York State mycology laboratories. The organism produced a white cottony colony and was identified by its unique zigzag conidiophore, thickened at the base. So far the corneal transplant has remained clear, with best visual acuity of 6/13 in the right eye.

Discussion

The genus *Beauvaria* comprises several common species of soil fungi that are pathogenic for insects. Interestingly, it holds a prominent place in historical microbiology. Bassi in 1835 demonstrated that beauvaria was the causative agent in producing the muscardine disease of silkworm.[1] This was the first demonstration of a micro-organism producing a disease process. In culture beauvaria grows as a white or slightly pigmented, fluffy to powdery colony. Microscopically the hyphae are narrow. The spore-bearing cells form single, irregularly grouped or radiating masses. A characteristic feature of this genus is the zigzag configuration which the spore-bearing tip assumes.[7]

Beauvaria first came to the attention of medical mycologists in the 1930s. Lichaa in 1933 and Langeron in 1934 reported the same case of keratoconjunctivitis in a 17-year-old Egyptian girl.[4 5] Langeron originally classified the fungus as *Beauvaria brumptii*. However, several years later

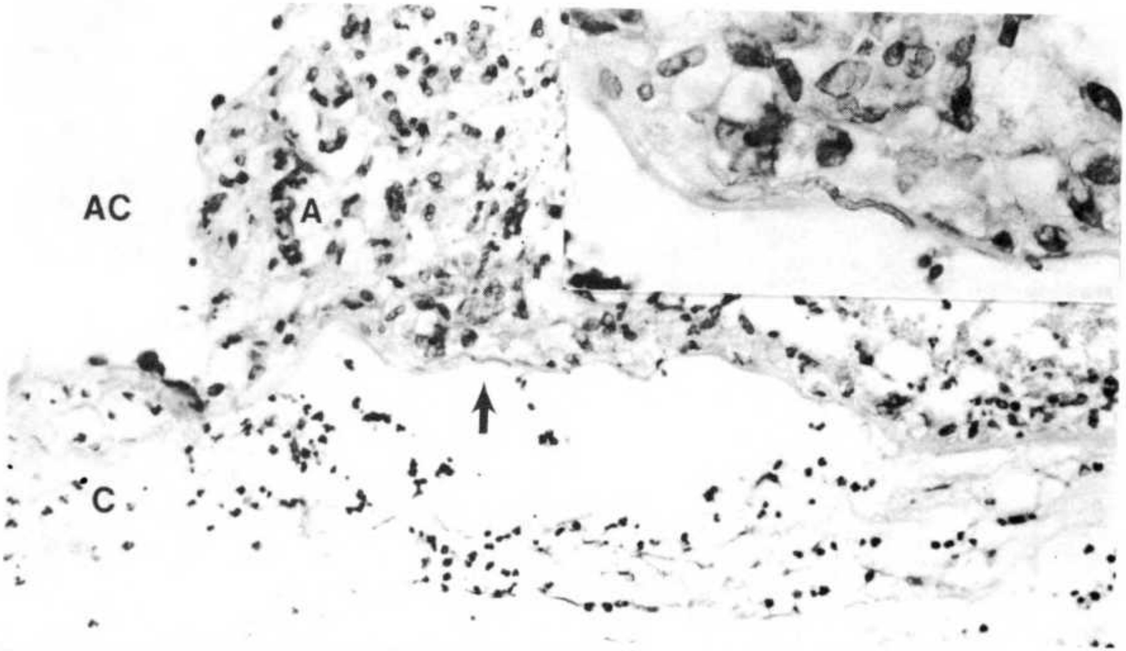

Fig. 1 *Histological section of the cornea showing fungus at Descemet's membrane (arrow and inset).* A=*abscess;* AC=*anterior chamber;* C=*cornea. (Haematoxylin and eosin, ×275; inset, ×688.)*

Langeron transferred it to the genus *Tritirachium* as *T. brumptii*. The case presented in this report represents the only reported instance of beauvaria producing ocular disease.

There are very few reports of beauvaria producing systemic disease in man. In 1966 Freour *et al.* reported a case of pulmonary disease in a 22-year-old woman in whom *B. bassiana* was isolated from surgically excised lung tissue.[2] In 1980 Drouhet *et al.* reported a case of osteoarthritis caused by beauvaria.[3]

Why did the fungus become pathogenic in our case? The history suggests that a corneal foreign body was present for several months and was very well tolerated. After its removal the corneal changes remained relatively unaltered on antibiotic drops. With both bacterial and fungal smears and cultures negative the patient was placed on a topical corticosteroid. After initial improvement the corneal process became more aggressive. Repeat cultures and corneal biopsy were negative for fungi. Corneal thinning progressed and eventually led to perforation.

Both antibiotics and steroids have been suspected of potentiating fungal infections of the eye. While antibiotic potentiation of oculomycoses has not been studied extensively, evidence has accumulated showing that some antibiotics may enhance fungal growth or potentiate fungual virulence. The investigation of corticosteroids has been more extensive. They not only enhance the virulence of pathogenic fungi but render saprophytic fungi pathogenic. Tissue resistance is also reduced by a number of mechanisms which depress the immune response and reparative processes. Numerous clinical and laboratory studies have been published on the effects of antibiotics and steroids in corneal and systemic processes[8-13]

We suggest that the addition of steroid in our case resulted in a more aggresive course of the infection, leading to perforation. Although initial attempts at fungal identification and culture proved negative, as in the present case, one's index of suspicion must remain high when the clinical setting suggests a fungal infection.

We thank Morris Gordon, PhD, for his expert advice and Norman Wald, MD, for referring the patient

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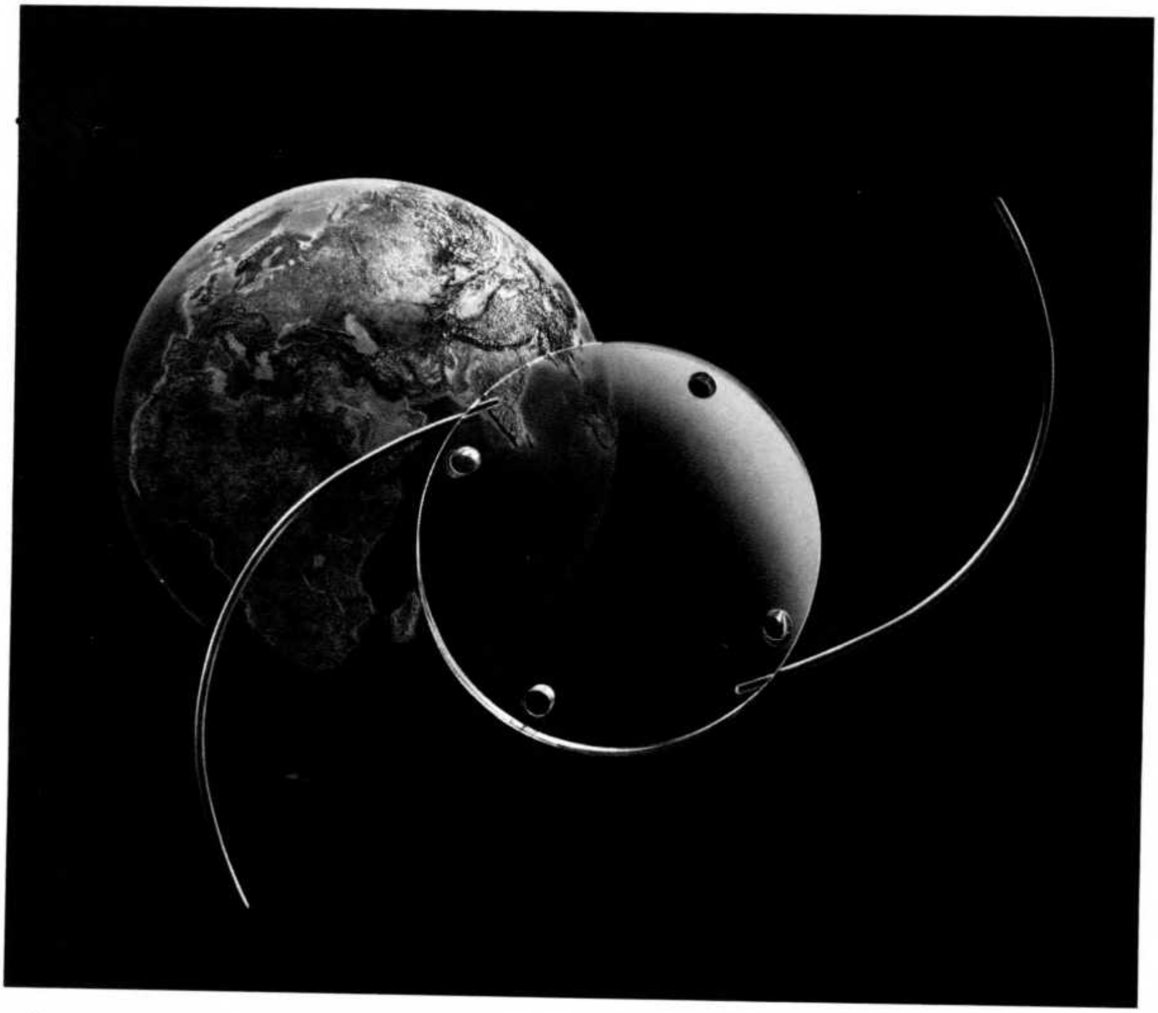

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British Journal of Ophthalmology, 1985, **69**, 551–554

Self-inflicted corneal injuries in children with congenital corneal anaesthesia

GRAHAM E TROPE, JEFFREY L JAY, JOHN DUDGEON,
AND GEOFFREY WOODRUFF

From the Tennent Institute of Ophthalmology, University of Glasgow, and the Royal Hospital for Sick Children, Glasgow

SUMMARY Severe corneal ulceration related to self-inflicted injury in the presence of congenital corneal anaesthesia is described in four boys under 2½ years of age. The ulcers had failed to heal until it was recognised that the children were scratching their own eyes. The application of arm splints allowed rapid healing. Although corneal ulceration is a recognised complication of congenital corneal anaesthesia, this preventable cause of the ulceration has not previously been recognised. In two cases there were isolated recurrences which healed quickly with the reapplication of splints. All four children had good vision initially, and, although there were no overt gross developmental abnormalities, two had neurological signs on detailed investigation suggesting cerebellar or brain stem malformation and one had unilateral anophthalmos, talipes equinovarus, and patent ductus arteriosus. All the children showed normal intellectual development. Whether the eye scratching behaviour was the primary cause of the ulceration or merely an aggravating factor, the identification of this abnormal behaviour is important in any child with idiopathic corneal ulceration, as even in the presence of congenital corneal anaesthesia the eyes heal quickly with effective splinting of the elbows. It is therefore important to test sensation of the cornea and face and to consider the possibility of self-inflicted injury in children with refractory corneal ulceration, as in our cases there were no other consistent diagnostic features.

Self-inflicted eye injury is an uncommon ophthalmic problem. It is recognised in blind children who rub their eyes to obtain vicarious light sensations from mechanical phosphenes and it occurs both in servicemen wishing to avoid military duty[1] and in civilian patients with psychological problems.[2] More severe ocular mutilation has been reported in psychotic adults[3] and mentally retarded older children.[4] Corneal ulceration is a recognised complication of congenital corneal anaesthesia,[5-8] but self-inflicted injury has not been recognised as its cause. This paper describes four young children with congenital corneal anaesthesia and corneal ulceration which failed to heal until measures were taken to prevent them putting their fingers into their eyes.

Patients and methods

Four cases presented in a six-year period and all were examined by a paediatric neurologist. This detailed neurological and developmental assessment revealed more associated abnormalities than were suspected at the initial clinical presentation, but all the children showed normal intellectual development.

CASE 1

A 1-year-old boy from a deprived social background was admitted to hospital with a central corneal ulcer in his right eye. He had been born with left anophthalmos associated with left sided facial microsomia, but the right eye was normal at birth. Closer examination revealed talipes equinovarus and patent ductus arteriosus. Sensation on both sides of his face appeared normal, but there was anaesthesia of the right cornea. His corneal ulcer healed slowly with topical therapy but relapsed six months later.

On his second admission he had a central corneal ulcer with hypopyon and Koch-Weeks bacillus sensitive to chloramphenicol was identified on bacteriological investigation. Despite specific antibiotic therapy the ulcer failed to heal until it was noted that

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he was rubbing the surface of the cornea with the tips of his fingers when left unattended. He was therefore placed in arm splints with the elbows extended, and this allowed the ulcer to heal rapidly, leaving a dense corneal scar which seven years later restricted vision to hand movements. He was intellectually above average.

CASE 2

A 2½-year-old boy was noted to be sticking his fingers into his eyes while being examined for suspected strabismus in the orthoptic department. The examination revealed no abnormality of vision or eye movement. Two weeks later he presented with a corneal ulcer in the right eye and associated abrasions of the forehead and periorbital skin. *Haemophilus influenzae* sensitive to chloramphenicol was isolated from the conjunctival sac, and the child was admitted to hospital for treatment, including splinting of his arms to prevent him from putting his fingers into his eyes. Detailed examination revealed traumatic depapillation of the anterior 2/3 of the tongue, with other oral signs of self-inflicted trauma. There was also partial anal atresia, cerebellar ataxia, cogwheel ocular pursuit movements, rotatory nystagmus, defective optokinetic nystagmus to both sides, bilateral corneal areflexia, and bilateral facial analgesia. Another notable feature was his fuzzy occipital hair. IQ tests were normal for his age.

This syndrome of cerebellar pathology, bilateral trigeminal anaesthesia, and peculiar occipital hair resembles the recently described cerebello-trigeminal and focal dermal dysplasia syndrome.[9]

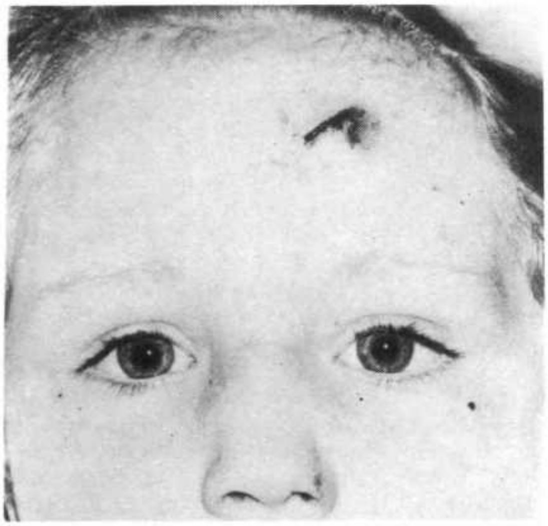

Fig. 1 *Case 2. Healing lacerations on the forehead and face after recognition and prevention of self-inflicted injury in bilateral trigeminal anaesthesia.*

The corneal and skin lesions healed quickly (Fig. 1) with one brief relapse affecting the left cornea a few weeks later. A minor opacity remained in this cornea, but after four years his visual acuity remained 6/6 in each eye unaided.

CASE 3

A 16-month-old boy presented with a corneal ulcer of the right eye. He had primary hydrocephalus, and a V-P shunt had been inserted when he was 5 months old. The ulcer failed to respond to topical antibiotics, and after a few days he was admitted to hospital for more intensive treatment. Corneal sensation was absent both on the ulcerated right eye and on the apparently normal left eye. Bacterial, viral, and fungal tests and conjunctival scrapings revealed no pathogens. Serum vitamin A, serum carotene, and leucocyte ascorbic acid estimations were normal. Despite hospital treatment the corneal ulcer increased in size.

Three weeks after admission an ulcer developed on the left cornea, and self-inflicted corneal abrasions were suspected, as he was seen to be putting his fingers into both eyes and scratching his eyelids (Fig. 2). He also tended to bang his head against the side of his cot when upset. The corneal ulcers and eyelid abrasions healed rapidly after elbow splints were applied to fix his arms in extension. After three weeks at home his mother discontinued the splints as he no longer seemed interested in rubbing his eyes. When examined six weeks later the eyelid skin and corneal epithelium remained soundly healed, but there was dense stromal opacity of the right cornea with minor localised opacity of the left.

Neurological assessment confirmed bilateral trigeminal analgesia as well as jerky ocular pursuit movement and ataxia suggesting brain stem and cerebellar malformation. However, a CT scan was normal, as was serum uric acid estimation.

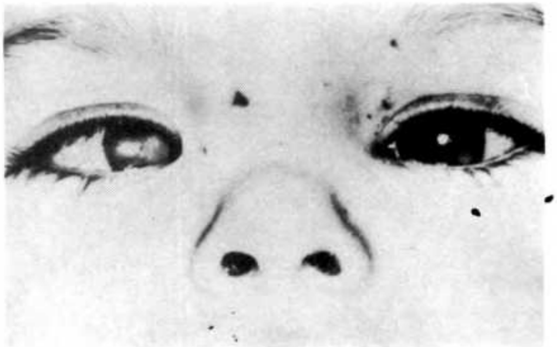

Fig. 2 *Case 3. Periocular skin abrasions and bilateral corneal ulceration (stained with fluorescein). These lesions were seen to be caused by self-inflicted scratching.*

Three years later there was a right convergent squint of 25° with a dense central corneal scar. The left eye recently developed a corneal ulcer precipitated, once again by self-inflicted abrasion. Reapplication of arm splints allowed healing but there was residual corneal opacity. His V-P shunt was still working well, his mental development was normal for his age, and he no longer displayed head banging behaviour.

CASE 4

An 18-month-old boy was admitted to hospital because of a central corneal ulcer of the right eye which had persisted for 11 weeks despite treatment. In hospital it was noted that he poked his fingers into his right eye even when it was covered by a pad and bandage, and his mother agreed that he sometimes banged his forehead and stuck his fingers into his eyes to seek attention. Corneal sensation was deficient in both eyes, and there was anaesthesia of the forehead and scalp back to the vertex. There were no other neurological signs and a CT scan, *x*-ray of skull, auditory evoked responses, and blood biochemistry including vitamin A and vitamin C levels were all normal. No pathogens were isolated from the ulcer on bacteriological, viral, and fungal culture.

Arm splints were applied, but, as he could sometimes remove them or rub his eyes on other objects, goggles were strapped to his face to provide further protection (Fig. 3). It was considered that the element of attention seeking behaviour in this child made it more difficult to control his eye rubbing. With these combined measures the ulcer healed within a few days. This child appeared to be hyperactive but was intellectually normal.

Discussion

It is difficult to be certain whether the eye scratching behaviour of these children was the primary cause of their corneal damage or whether it arose secondarily to another corneal disturbance. Case 2 was certainly seen to be putting his fingers in his eyes before the development of corneal ulceration. Moreover, these four boys with corneal anaesthesia would seem unlikely to have suffered much discomfort should there have been another primary cause of corneal ulceration and might therefore seem to have little cause to rub their eye. On the other hand that same anaesthesia may have allowed them to rub the cornea without pain when other symptoms such as watering or reduced vision had made them aware of ocular disturbance. P Wright (personal communication) has observed adult patients with acquired trigeminal anaesthesia produce excoriation of the cheek because of an insuperable feeling of needing to rub the analgesic area. Some of us may have noted a similar sensation following regional anaesthesia for dental surgery.

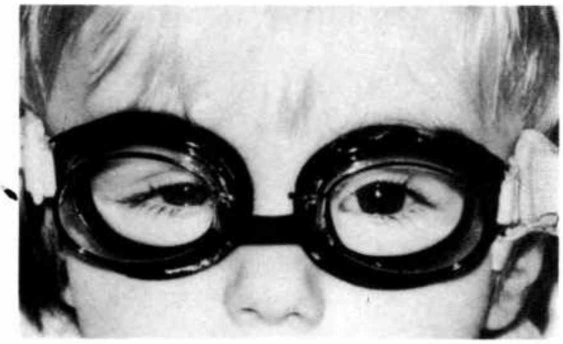

Fig. 3 *Case 4. Goggles strapped to the face were required in addition to arm splints as he tried to rub his eyes on extraneous objects when his arms were splinted.*

The cause of isolated congenital corneal anaesthesia remains obscure, though it may be associated with more widespread abnormalities such as the obvious maldevelopment of the face and skull in the Goldenhar-Gorlin syndrome,[10] the generalised indifference to pain of familial dysautonomia (Riley-Day syndrome),[11] or as part of the condition of congenital universal insensitivity to pain.[12] None of our patients had these conditions, but it is interesting to note that two of them (cases 2 and 3) had clinical evidence of mild brain stem or cerebellar maldevelopment, features which have not previously been associated with congenital corneal anaesthesia. In case 1 it is possible that the emotional disturbance arising from a difficult maternal relationship (the mother later abandoned the child) induced either the eye rubbing behaviour or a type of temporary functional corneal anaesthesia or both. It seems that functional corneal anaesthesia can occur in adults with keratitis artefacta.[2] Severe and generalised self-inflicted mutilation does occur in children, but these patients usually have an underlying biochemical disorder as in the Lesch-Nyhan syndrome,[13] the Cornelia de Lange syndrome,[14] and the Gilles de la Tourette syndrome,[15] but congenital corneal anaesthesia is not a feature of these cases.

Whatever the theoretical considerations, it appears that self-inflicted corneal abrasion in infants may be more common than is recognised and should always be considered as a cause of intractable corneal ulceration in this age group, especially as the presenting feature of corneal anaesthesia. There were no other consistent diagnostic features in our cases, though scratches on the face were a useful clue in two of them.

We have found that effective splinting of the child's arms with elbows extended (permitting short, supervised periods of free mobility), allows rapid healing when combined with appropriate topical antibiotic therapy. In case 4 the attention seeking behaviour combined with corneal anaesthesia made effective protection of his corneas more difficult, and he required the addition of goggles to prevent him from rubbing his eyes on extraneous objects when his arms were splinted. Although the ulcers in all our patients healed soundly within a few days of effective protection being applied, the later relapses in cases 2 and 3 indicate the need to advise the parents of the risk of recurrences so that effective measures can be taken to limit the corneal damage if the eye scratching behaviour reappears.

We thank Dr John Stephenson for neurological assessment of these children, Dr J S Cant for allowing us to examine patient 4, and Mrs J Murray for secretarial assistance Dr G E Trope was supported by the Frost Foundation

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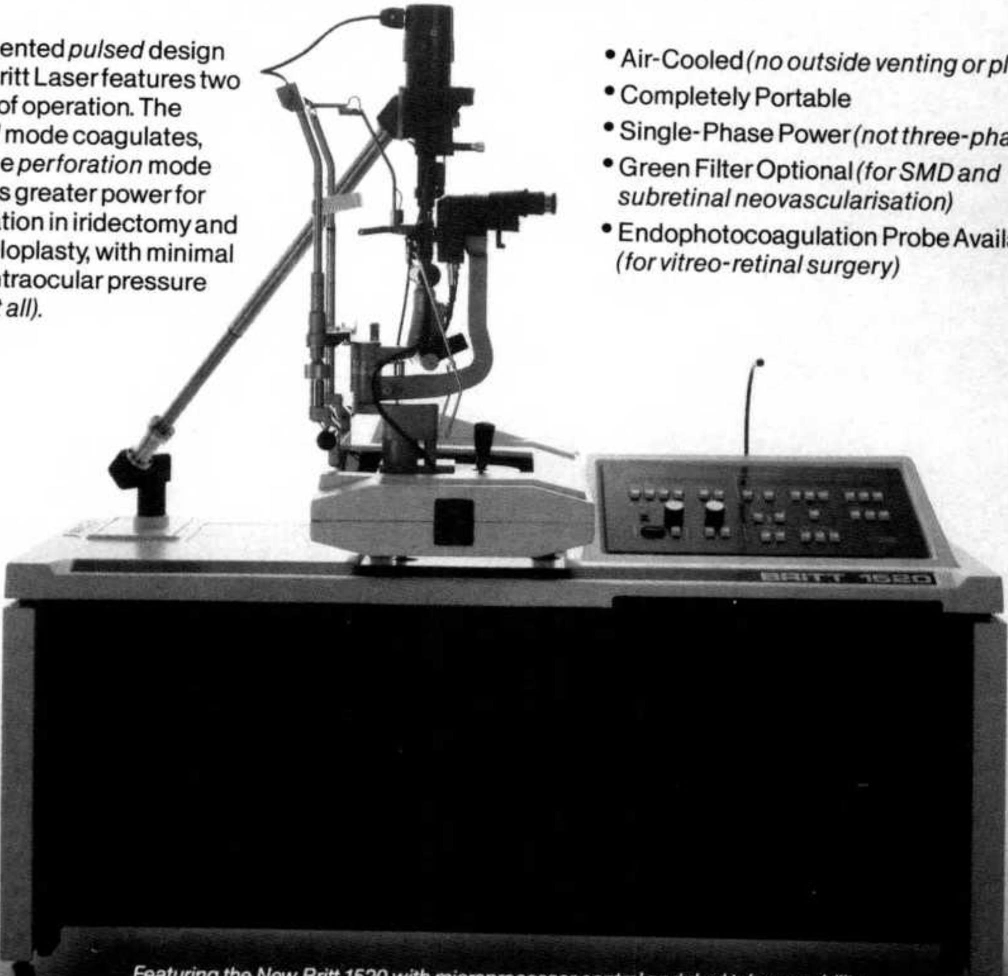

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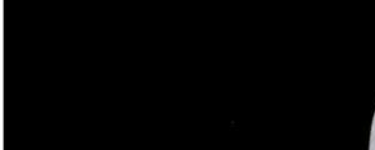

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Book reviews

Atlas of the Peripheral Retina. By FRANK C BELL AND WILLIAM J STENSTROM. Pp. 232. £73·50. Saunders: London. 1983

This book is an extensive atlas combined with the relevant text to describe most of the ocular conditions affecting the retinal periphery. There are chapters on basic anatomy, peripheral retinal appearances and degenerations, retinal detachments, benign and malignant tumours, infective and inflammatory retinal diseases, retinal vascular diseases (particularly diabetic retinopathy), the phakomatoses, and medical retinal diseases

The production is to a very high standard; pictures of the retinal paintings are fairly diagrammatic. The authors have indicated that it is their intention to prepare a book for the general ophthalmologist. One wonders whether such a book is in fact useful to such a practitioner, or whether it would have been better to include in an atlas of this type the more common disorders, affecting primarily the posterior pole of the eye, particularly those that have a profound effect on vision (e g , the macular degenerative group) The avoidance of purely central retinal lesions makes for an odd balance in the book. For example conditions mainly affecting the central retina, but which do have some peripheral extension, are included (e g., diabetic retinopathy and angioid streaks) I felt that the chapters dealing with peripheral retinal degeneration and basic anatomy were particularly effective and those dealing, for example, with retinal detachments less so (it was surprising to see three diagrams dealing with giant retinal tears).

This book is extremely expensive and will not find a place on the bookshelf of the general ophthalmologist, for whom it is intended However, residents in training with access to hospital libraries will find that it will be a useful addition, as a ready means of familiarising themselves with some of the fascinating complexities of the retinal periphery

ANTHONY CHIGNELL

Bucherei des Augenarztes. Vol. 98. **Pathophysiologie des Sehens.** Edited by VOLKER HERZAU. Pp. 244. DM 58·00. Stuttgart. 1984.

This volume, the 98th in the series 'Bucherei des Augenarztes,' comprises a collection of 28 papers presented at the symposium on the pathophysiology of vision held at Tubingen in May 1983 The edited version contains some of the discussion also

There are four sections dealing with the retina and optic nerve, supragenicular pathways, clinical electrophysiology, and binocular vision. The emphasis in most of these contributions is on experimental rather than clinical ophthalmology, and the book is therefore more likely to appeal to the research worker The articles are in German but are provided with short summaries in English With such a varied subject matter and authorship it is hard to single out any distinctive features of this volume, but the section on the retina and optic nerve covers a number of interesting pathophysiological topics which have clinical relevance

T J FFYTCHE

Bücherei des Augenarztes. Vol 99. **Theorie und Praxis der modernen Schielbehandlung.** Eds. GERD MEYER-SCHWICKERATH AND KLAUS ULLERICH. Pp. 315. DM 76·00. Enke: Stuttgart. 1984.

The 99th volume in the series 'Bucherei des Augenarztes' is devoted to the subject of squints and is to be warmly recommended for postgraduate reading. The editors have commissioned 24 contributions from various authors on all aspects of ocular motility, including chapters on history, anatomy, physiology, diagnosis, investigation, and therapy These blend together very satisfactorily to form a comprehensive book on the subject.

The book is well illustrated with diagrams and black-and-white photographs, and the references are extensive. All chapters are in German, but although each is provided with a short English summary the full impact of the book can be realised only by reading the text itself For this reason this volume is unlikely to have a wide readership among ophthalmologists who do not understand German, and this is unfortunate in view of its excellence

Once again this popular series of ophthalmic textbooks has produced a volume of very high standard, and the editors are to be congratulated. One looks forward eagerly to the next century of contributions.

T J FFYTCHE

Neurology and Neurobiology. Vol. 9. **Development of Visual Pathways in Mammals.** Eds. JONATHAN STONE, BOGDAN DREHER, DAVID H RAPAPORT Pp. 489. £52·00. Alan R Liss: New York. 1984.

This is a collection of 31 papers given at a symposium on visual development held in Sydney in 1983 The papers cover a wide spectrum of topics representing the current research on visual pathway development, and although many of the results are already familiar the book provides a useful summary of the field.

The first section, entitled 'Development of the retina and optic nerve,' is concerned mainly with the development of retinal topography in the ganglion cell layer The authors come to the interesting conclusion that the development of regional specialisation depends on differential growth and transformation of cell types rather than cell death and generation In the second section, on the development of visual connections and neuronal structure, physiological and anatomical studies are described which show broad patterns of visual projections contracting during maturation to the specific differentiated patterns in the adult The papers also deal with plasticity where the normal differentiation and contraction is modified—for example, by an unusual pattern of visual stimulation. Studies on the normal development of the lateral geniculate nucleus provide evidence for the differential rates of maturation of relay cells and the reduction of retinal synaptic contacts which occur during development The third section, dealing with the reorganisation of visual pathways following damage or transplantation, describes both degeneration and reorganisation, showing the plasticity of visual pathways. The results of these studies show that the degree of compensation which will occur after damage to the pathway depends on the age at which the damage has occurred. The final section of the book deals with the environmental modification of the visual system New examples of environmental effects are described—for example, on the postnatal growth of cells in the W cell relay of the lateral geniculate, on cortical orientation selectivity, and on ocular dominance in areas 18 and 19 Papers also examine the potential for recovery from environmental modifications, for example, by reverse occlusion of monocularly deprived animals New work on the maturation of the rabbit and primate visual cortex is presented.

This book provides a good review of the research under way on the development of visual pathways and is most suitable for those already working in this area.

B P HAYES

Atlas of the Ocular Fundus. Third edition. By H SAUTTER, W STRAUB, R TURSS, H ROSSMANN. Pp. 188. £78·00. Pitman: London. 1984.

This is a beautifully produced book It contains high quality colour photographs of common fundus conditions with fluorescein angiography pictures printed where relevant The descriptions are elegant, and in some case treatment is described. Some of the nomenclature does not coincide with that used in England and America. For example, they use the term arteriosclerotic-chorioretinopathy for disciform macular degeneration. The only common fundus conditions omitted are macroaneurysms and a few less common conditions, such as presumed ocular histoplasmosis and Vogt-Koyanagi-Harada syndrome.

The only criticism I have with the treatment sections is that the authors tend towards focal treatment quite frequently for retinal new vessels, which is contrary to the British experience, where more peripheral retinal ablation is used

This is a good atlas for any ophthalmologist and would be useful for physicians It would be a good investment for any large medical library. The price is rather high for the individual ophthalmologist.

RONALD J MARSH

Major problems in Clinical Pediatrics. By LEONARD B NELSON. Pp. 268. £42·00. Saunders: London. 1984.

This book was written for paediatricians, general practitioners, house officers, and others concerned with the welfare of children, and it succeeds in its aims It is laid out conventionally, discussing the various aspects of paediatric ophthalmology on a mainly anatomical scheme There are chapters on visual development and ocular examination, which are practical, but perhaps a little high powered for the non-ophthalmologist. For instance, it seems a little much to expect the paediatrician to be interested in descriptions of slit-lamp examination or indirect ophthalmoscopy except to satisfy his curiosity There is a chapter on the visually handicapped child which is directed towards the older child and offers little advice about early intervention.

The book is well if not always accurately referenced, and there are numerous illustrations, most of which are borrowed from two well-known textbooks It is sad that exchange rates will put this book out of the reach of most private buyers, but it will find its way on to hospital library shelves, where it will be dipped into by many doctors who look after children.

DAVID TAYLOR

I Glaucomi Secondari. Eds. F PONTE, L SCULLICA, C BISANTIS. Pp. 527. No price given. Clinica Oculistica: Messina, Italy. 1983.

This textbook on secondary glaucoma is written by the three main authors, nine collaborators, and 31 assistants, all from the Universities of Palermo and Messina A substantial historical introduction is followed by a chapter on the definition and the classification of the secondary glaucomas which is adopted in the book The intrinsic ocular causes are dealt with in the first chapters, pseudoexfoliation glaucoma and neovascular glaucoma receiving extended treatment An approximately equal space is devoted to the systemic associations of secondary glaucoma. An outstanding feature of the book is its abundant bibliography, perhaps rather loaded towards the Continental and, more particularly, the Italian literature; however, the Anglo-Saxon sources, where fundamental, are adequately represented

The material is well presented in spaciously set out pages, and the illustrations are mostly of a high standard.

JOHN ROMANO

Notes

Medical management of ocular inflammations

A national symposium on 'Recent and controversial aspects of the medical management of ocular inflammations' will be held at Jodhpur on 16–18 November 1985 Further details from the chief organiser, Professor M R Jain, Department of Ophthalmology, Dr SN Medical College, New Teaching Hospital, Jodhpur 342 003, India Registration fee 25.00 US dollars

Contact lens technology

The Cullen Eye Institute, Baylor College of Medicine, will hold its 26th Annual Course in Contact Lens Technology 5–7 December 1985 at the Intercontinental Hotel in Houston, Texas This course is open to all ophthalmologists, residents, and fellows in ophthalmology, and technicians sponsored by an ophthalmologist. It will include lectures, practical demonstrations, and student participation in 25 areas of contact lens technology. Details from Bette McAinch, Contact Lens Technology Course, Cullen Eye Institute, Baylor College of Medicine, Houston, Texas 77030, USA

Cyclops Society

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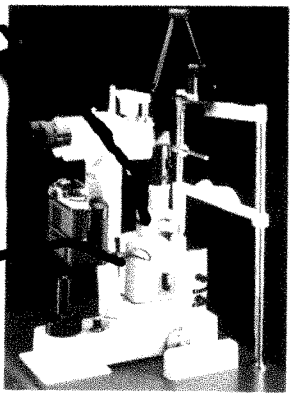

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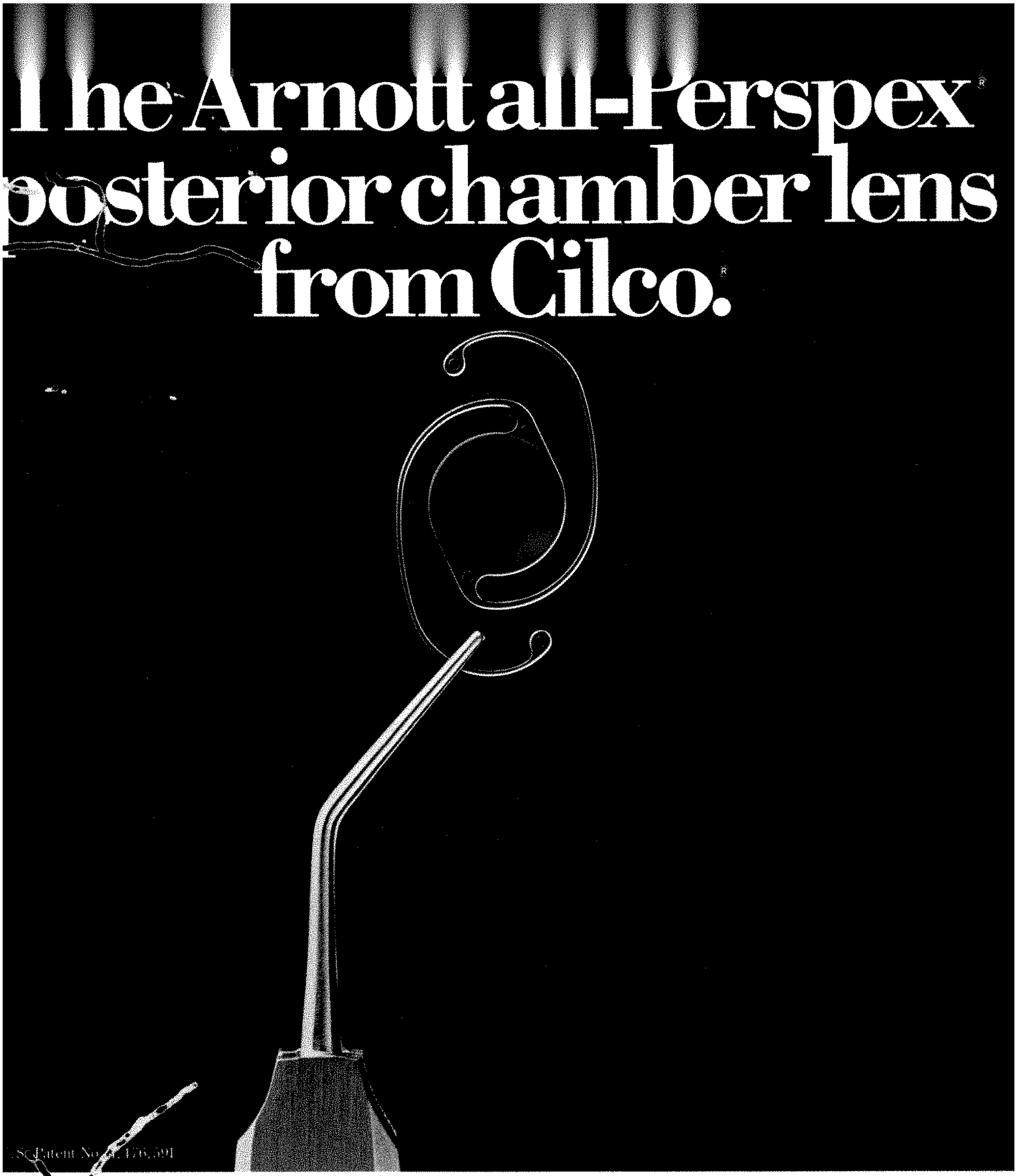

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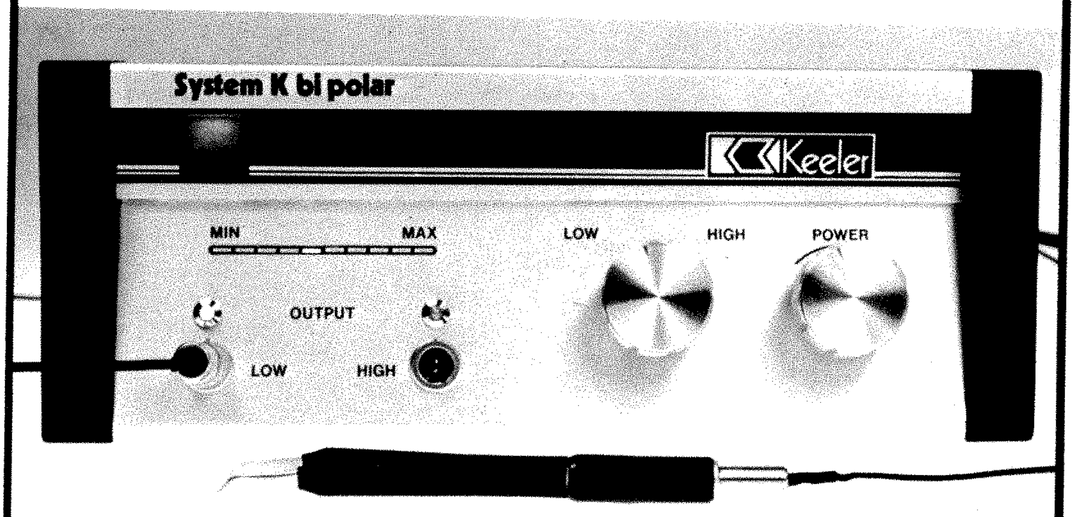

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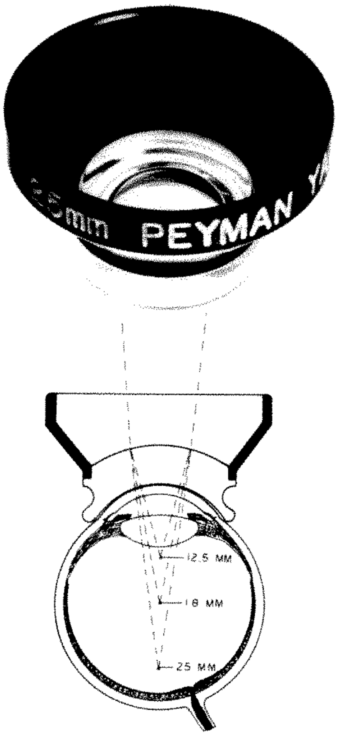

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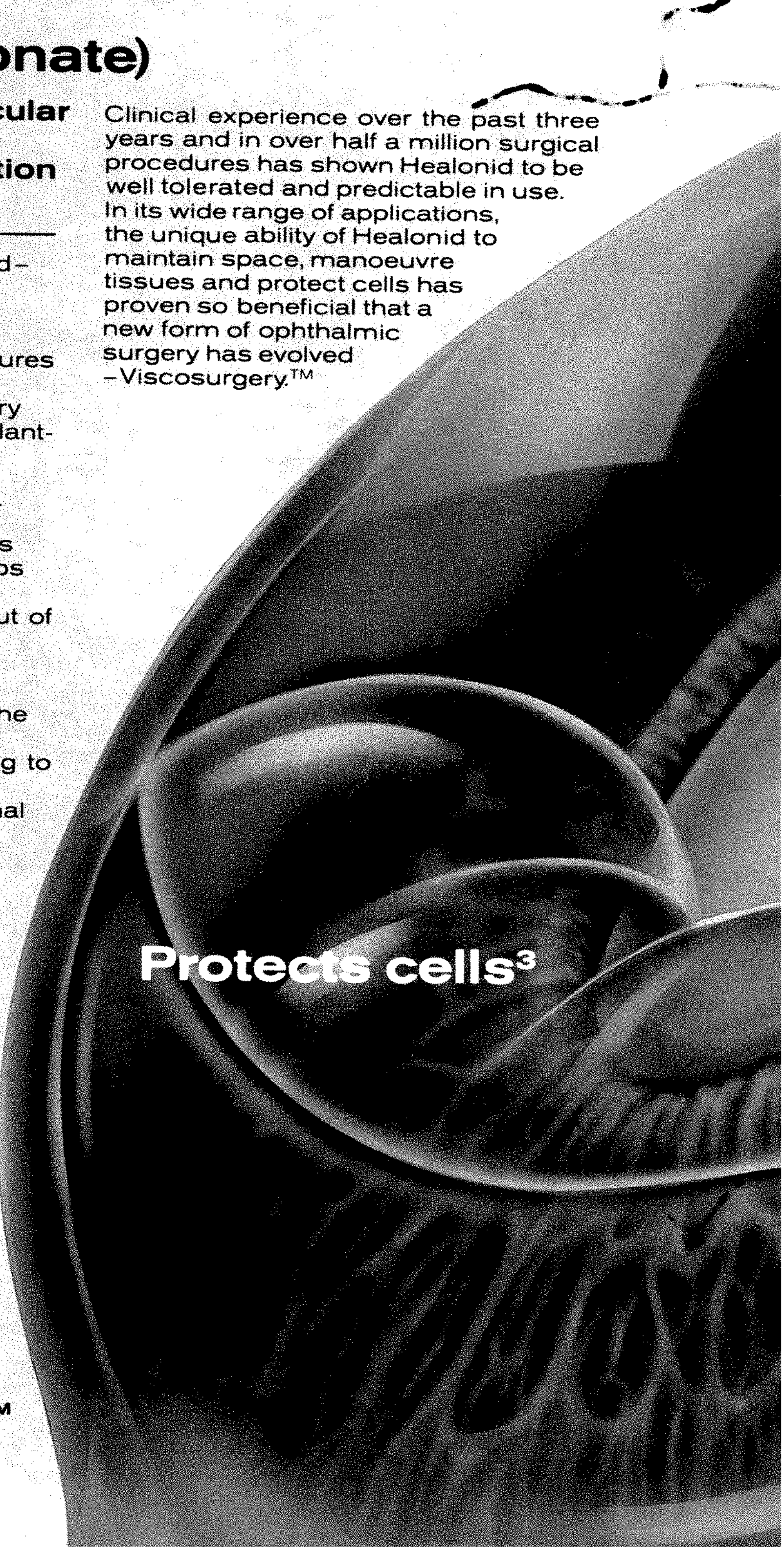

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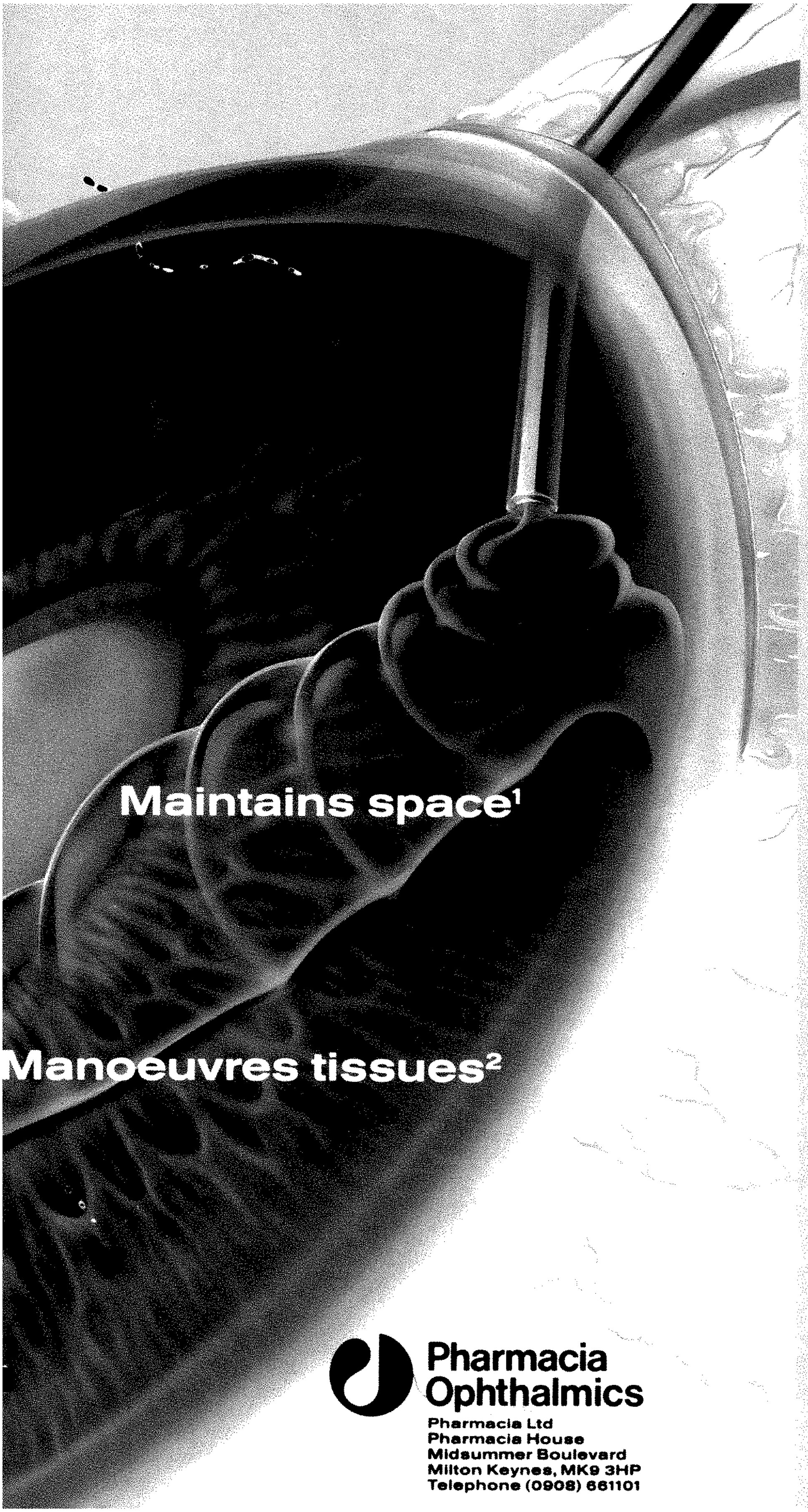

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British Journal of Ophthalmology, **69**, 557–561

Orbital rhabdomyosarcoma: improved survival with combined pulsed chemotherapy and irradiation

SALAHUDIN Y A GHAFOOR[1] AND JOHN DUDGEON[2]

From the [1]Tennent Institute of Ophthalmology, University of Glasgow, and the [2]Royal Hospital for Sick Children, Glasgow

SUMMARY Three cases of embryonal orbital rhabdomyosarcoma are presented in which two cases had intracranial extension. All three are alive and well on follow-up several years after completing a 12-month course of combined pulsed chemotherapy and irradiation. The improved prognosis even in parameningeal involvement is emphasised.

Although orbital rhabdomyosarcoma is the commonest primary orbital tumour in childhood, it is still a rare condition for the practising ophthalmologist, with an annual incidence of 1 in 4·4 million. Combined pulsed chemotherapy and radiotherapy has improved the survival rate when lesions are confined to the orbit to 90% in contrast to 66% with radiotherapy alone.[1] With bone destruction and extension, however, the overall survival with the combined therapy is 65%. In cases that failed to respond satisfactorily death usually occurred within 18 months.

The modern approach to a child presenting with suspected rhabdomyosarcoma is early diagnosis by biopsy, accurate pretreatment staging, local control of the primary tumour, and eradication of micrometastases. The combined use of the antimetabolite vincristine, antitumour antibiotics actinomycin D and adriamycin, and the alkylating agent cyclophosphamide following irradiation, has permitted more complete tumour eradication in the orbit and suppression of potential metastasis. An interdisciplinary team approach in the management of such cases is essential.

We report three cases which presented in the West of Scotland. All three patients are alive and well after completing a 12-month combined therapy course (Table 1).

Case reports

CASE 1

An 8-year-old girl presented on 28 September 1979 with painful proptosis of the right eye and marked chemosis as well as restriction of movement on dextroversion (Fig. 1). The visual acuity in the right eye was 6/6 and in the left 6/9. A retrobulbar mass was suspected; a biopsy proved the lesion to be a rhabdomyosarcoma. *X*-ray of the orbit, tomography, ultrasound, and CT scan disclosed destruction of the lateral wall and inferior margin of the right orbit as

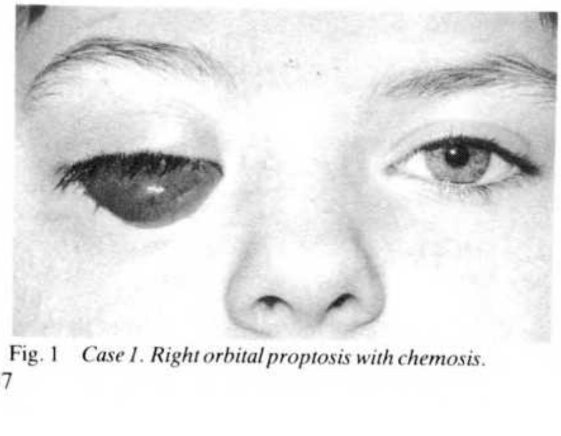

Fig. 1 *Case 1. Right orbital proptosis with chemosis.*

Table 1 *Survival of rhabdomyosarcoma patients*

Case	*Age*	*Sex*	*Histology type*	*IRS stage**	*Survival Since diagnosis†*
1	8	F	Embryonal	IIB	5 yr
2	7	M	Embryonal	III	3 yr 8 mo
3	3	M	Embryonal	III	4 yr 10 mo

*IRS=Intergroup Rhabdomyosarcoma Study.
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Correspondence to S Y A Ghafoor, FRCS Glas, Tennent Institute of Ophthalmology, University of Glasgow, Western Infirmary, Glasgow G11 6NT.

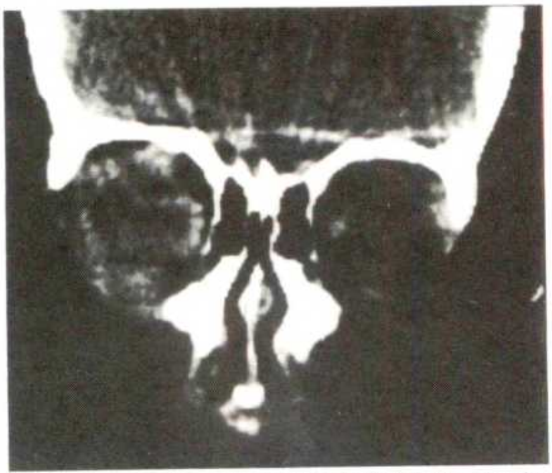

Fig. 2 *Case 1. CT scan (coronal section) showing extension of orbital lesion laterally.*

well as that of the lateral wall of the right antrum and malar bone (Fig. 2). Screening tests for metastasis included skeletal survey, chest *x*-ray, blood smears, liver scan, bone scan, abdominal ultrasound, liver and spleen scan, and bone marrow trephine.

The lesion was staged IIB according to the American Intergroup Study classification.[2] Initial weekly chemotherapy consisted of vincristine (1·5 mg/m^2 intravenously), adriamycin (40 mg/m^2 intravenously) and cyclosphosphamide (200 mg/m^2 intravenously). After two doses radiotherapy was given to the residual tumour at a dose of 4000 rads. Pulsed chemotherapy with vincristine, cyclophosphamide, and adriamycin intravenously was given at fortnightly intervals until the total dose of adriamycin was 400 mg. There was a pause of two weeks between radiotherapy and recommencement of chemotherapy, then a fortnightly regimen intravenous of vincristine (1·5 mg/m^2), cyclophosphamide (400 mg/m^2), and Actinomycin D (1·0 mg/m^2) was continued for a year.

The size of the tumour was monitored with serial CT scans. The ocular side effects initially were of a local nature, with eyelid skin reactions and conjunctival chemosis, but the right eye continued to be irritable, with marked corneal destruction, neovascularisation, and painful uveitis. Five months later it was still unresponsive to intensive therapy and was enucleated. No evidence of extension into the sinuses was found at operation. Pathological examination by light and electron and microscopy showed the lesion to be an embryonal rhabdomyosarcoma. A fuller account of the ultrastructure of this case has been reported elsewhere.[3] In this study a close resemblance was found between the ultrastructural appearance of the undifferentiated rhabdomyosarcoma cells lacking the z banding found in this tumour and that of the primitive mesodermal cells in the extraocular. muscle of a 9–10 cm human embryo.

On completion of the chemotherapy regimen the right socket was markedly contracted, and cosmetic reconstruction with dermofat graft was successfully done. Later side effects included recurrent epistaxis and sinusitis.

CASE 2

A 7-year-old boy presented in February 1981 with a painful right eye and two days later developed proptosis, ptosis, and limited ocular movement on adduction. The condition was initially thought to be related to ocular trauma sustained two days earlier.

The visual acuity in the right eye was only hand movements and in the left eye was 6/6. In four days the right visual acuity deteriorated to no perception of light, and the right disc had become swollen. Right orbitotomy biopsy showed the swelling to be an embryonal rhabdomyosarcoma. CT scan showed this intraorbital lesion to be associated with erosion of the posterior and inferior orbital walls and maxillary antrum as well as intracranial extension into the middle cranial fossa. Investigations excluded metastasis to the lungs, skeleton, bone marrow, and cerebrospinal fluid. By the staging criteria of the American Intergroup Rhabdomyosarcoma Study the disease was classified as stage III.

Initial radiotherapy to the cranium only was given in a dose of 3000 rads over four weeks, followed by 2500 rads to the right orbit and cavernous sinuses over three weeks. Intravenous pulsed chemotherapy with vincristine (1·6 mg/m^2), cyclophosphamide (200 mg/m^2), and actinomycin D (0·3 mg/m^2) was followed by methotrexate (12 mg), cytosine arabinoside (50 mg), and hydrocortisone (25 mg). In addition intrathecal hydrocortisone (25 mg), methotrexate (12 mg), and cytosine arabinoside (50 mg) were administered at weekly intervals for eight weeks. Tumour regression was noted and monitored with CT scan. Six months later, however, the right eye developed painful keratitis, and on suspicion of endophthalmitis it was eviscerated. The chemotherapy regimen was continued until March 1982. Follow-up since then has shown no recurrence of the lesion. General side effects of this regimen included infection and stomatitis. Impairment of gait was attributed to vincristine neuropathy.

CASE 3

A 3-year-old boy presented in January 1980 with a two-week history of swelling over the right eyelid and proptosis. Four days later a tense mass in the upper lateral aspect of the orbit with displacement of the

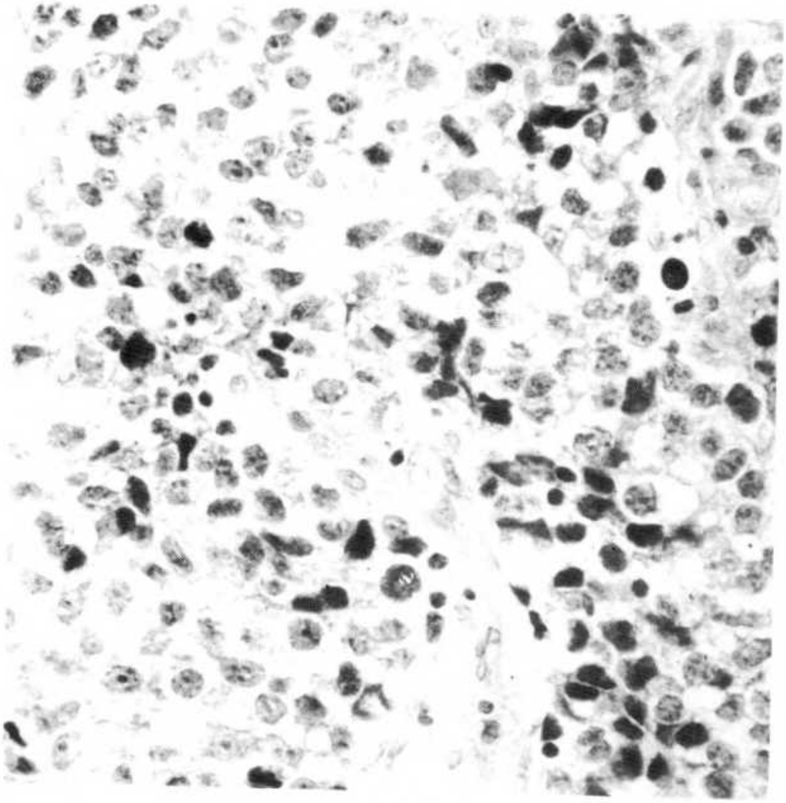

Fig. 3 *Case 3. Histology of embryonal rhabdomyosarcoma. (Haematoxylin and eosin, × 450.)*

globe was noted. *X*-ray showed an enlarged orbit. Anterior orbitotomy exploration revealed a pearly mass lying subperiosteally with bone destruction in the superolateral region of the orbit. Biopsy showed this to be an undifferentiated rhabdomyosarcoma (Fig. 3). A CT scan showed in addition extension to the middle cranial fossa and temporal fossa (Fig. 4). These findings staged the lesion as stage III according to the criteria of the American Intergroup Rhabdomyosarcoma Study. Initially two courses of chemotherapy at weekly intervals with intravenous vincristine (1·0 mg/m^2) were followed by radiotherapy. The total dose was 5000 rads spread in a fractionation pattern suitable to the child's age over a period of 67 days. External megavoltage irradiation with a high energy (4 MeV) beam enabled the use of a sharp beam edge. Concurrently five weekly intravenous pulses of vincristine and cyclophosphamide at the above doses were administered, followed by 10 monthly intravenous pulses of adriamycin (total dose 260 mg), vincristine (1·5 mg/m^2), and cyclophosphamide (400 mg/m^2). The systemic side effects that occurred were those of abdominal pain, neutropenia and minor attacks of epistaxis. Serial CT scans showed regression of the cranial lesion and a small residual lesion at the orbit. On completion of the chemotherapy course in February 1982 no extension of the lesion was noted, but a posterior subcapsular cataract in the right eye developed. Extracapsular extraction of cataract with lens implantation was done.

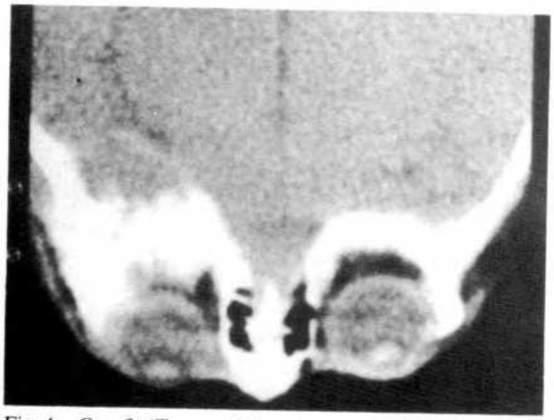

Fig. 4 *Case 3. (T scan axial section) showing extension of orbital lesion into adjacent parameningeal tissues.*

Discussion

Orbital rhabdomyosarcoma in children is of the embryonal type, and our three cases show the expected age incidence. The postulated origin of these tumours is from pluripotential mesenchymal elements. The commonest site of the lesion was emphasised by Frayer and Enterline[4] as the superonasal quadrant of the orbit, but in two of our cases it was superotemporal. A history of trauma may lead the unwary to exclude the possibility of rhabdomyosarcoma. The differential diagnosis usually included infantile haemangioma, leukaemia, and neuroblastoma. Urgent biopsy is essential; the unequivocal diagnosis of embryonal type is possible only by electron microscopy demonstration of thick myosin filaments in the cytoplasm of rhabdomyosarcoma.[5]

Although extension to paranasal sinuses occurred in all three cases and also intracranial extension in two, there was complete regression following combined chemotherapy, leaving only a small residual 'lesion' in one case. Serial monotoring has not shown any evidence of activity.

Knowles *et al.*[6] reviewed 162 cases of the four major series published on orbital rhabdomyosarcoma constituting 75% of the literature and found only 49 patients (25%) who survived more than three years. Primary rhabdomyosarcoma in the orbit is uncommon compared with its incidence in other sites of the body. Jaffe *et al.*[7] found only eight children (13%) with orbital rhabdomyosarcoma in a series of 61 children affected by the tumour. Five out of these eight children with orbital lesions were alive over two and a half years later after combined orbital exenteration (radical neck dissection in three cases), radiation therapy, and actinomycin D (occasionally vincristine). Of these survivors three were stage II and two were stage I. The overall survival rate in Jaffe *et al.*'s series was best for primary orbital lesions (63%) compared with the poorer prognosis of rhabdomyosarcoma in other sites. Sutow *et al.*[8] found better survival rates (91%) in their series in the Intergroup Rhabdomyosarcoma Study (IRS). In this series orbital lesions were found in 26% of patients with rhabdomyosarcoma. It has generally been agreed by those reporting this tumour[9] that a long-term survivor is a patient alive two years after diagnosis is made. By this definition our findings confirm such a good prognosis (Table 1).

Extension into parameningeal sites occurred in two cases. The CT scan is one of the best investigative tools not only for delineating the extent of such involvement but also for monitoring the effects of treatment. The importance of adequate treatment at this site cannot be overemphasised, as the meninges constituted the initial site of the disease recurrence.[10] Primary rhabdomyosarcoma of the midcranial fossa itself is extremely rare.[11]

Recent multiple therapeutic approaches which aim to conserve the eye with a planned programme to treat each case in an individual manner should give an even better prognosis.[12] However, complications continue to occur with each type of treatment. Radiation keratitis and suspected endophthalmitis led to enucleation and evisceration in two of our cases. A contracture socket deformity needed further reconstruction. The systemic side effects of cytotoxic drugs included epistaxis, neutropenia, abdominal pain, and stomatitis, and in one case neuropathy due to vincristine.[13] One could only speculate that perhaps the longer duration of the irradiation fractionation pattern was beneficial in case 3.

Long-term complications of radiotherapy as a treatment of rhabdomyosarcoma have not been reported for orbital lesions, though reports of osteogenic sarcoma of the mandible and hypopituitarism after irradiation of nasopharyngeal rhabdomyosarcoma exist.[7]

Future developments in the management of this condition reside in reducing the toxicity of the present chemotherapeutic drugs.[14] A recent approach involves the use of drugs to block the renal and bladder toxicity of cyclophosphamide. Another approach uses drugs such as lithium carbonate to stimulate the marrow production of leucocytes, thus reducing the marrow suppression of cytotoxic drugs. It has also been suggested that the development of analogues may reduce the toxicity of the active structure of cytotoxic drugs used in the treatment of rhabdomyosarcoma in children. The use of folic acid 'rescue' following massive doses of methotrexate is still under investigation and its value is unproved.

The authors thank Drs I M Hann and A A G Gibson and the Royal Hospital for Sick Children for their valuable advice and criticism, Dr Gibson for the photomicrograph and the Department of Medical Illustration, RHSC, for the photographs, and Miss Lorna Gow for typing the manuscript

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British Journal of Ophthalmology, **69**, 562–566

Sarcoidosis with infiltration of the external ocular muscles

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SUMMARY This is a clinicopathological report of a patient with systemic sarcoidosis who had infiltration of the external ocular muscles, Tenon's capsule, and lacrimal glands.

Sarcoidosis is recognised as a multisystem disease of unknown aetiology in which non-caseating granulomas are found in the individual organs and the clinical presentation depends on site, quantity, and duration of the granulomatous infiltration within the affected organ. About 25% of patients with sarcoidosis have ophthalmic involvement manifested either by infiltration of the ocular adnexa, intraocular inflammation, or infiltration of the retrobulbar visual pathways. Orbital disease with sarcoidosis is rare. We have seen occasional patients presenting with orbital apex or cavernous sinus syndromes, but a discrete orbital granuloma or myositis appears to be exceptional.

In a review of the ophthalmic manifestations of sarcoidosis Obenauf *et al.* recorded orbital disease in only two out of 532 patients, but did not describe these cases further.[1] Trokel and Hilal reviewed 70 cases of orbital myopathy diagnosed from CT scan appearances, but did not have any cases of sarcoidosis in their series.[2] In contrast, skeletal muscle myopathy with sarcoidosis is well recognised and presents in overlapping patterns of palpable muscle nodules, acute polymyositis, or a chronic myopathy.[3-5] The majority of these patients are asymptomatic, and it is possible that the incidence of skeletal muscle disease is underestimated, as biopsies are rarely performed on asymptomatic patients. Some authors have estimated that 50% or more of patients with systemic sarcoidosis have histologically identifiable granulomata between normal muscle fibres.[5 6]

We present a case history with CT scans, operative photography, and confirmatory histology of a patient with marked sarcoid infiltration of an external ocular muscle.

Case report

In May 1980 a 39-year-old West Indian man presented to the Ophthalmic Department of St Thomas's Hospital with a one-month history of a lump in the outer aspect of the upper eyelid, which had been slowly enlarging and had recently been tender to touch. He had no visual disturbance and, other than occasional aching in his chest, no other systemic symptoms.

On examination he was a fit man with normal cardiovascular, respiratory, and abdominal systems. There were a few shotty, slightly tender lymph nodes in his right groin. His visual acuities were 6/5 in either eye. There was a soft, mobile mass in the outer aspect of the left upper eyelid (Fig. 1), which had the clinical features of a lacrimal gland swelling. There was no displacement of the globe, and eye movements were full in all directions. Examination of the anterior segments and fundus was normal.

Although an *x*-ray of the skull and orbits showed no abnormality, a chest *x*-ray demonstrated right-sided hilar lymphadenopathy, which was confirmed by hilar tomography and was compatible with a diagnosis of sarcoidosis. Routine haematological and biochemical analyses were all normal, apart from showing sickle cell trait with a haemoglobin phenotype of Hb SA. Mantoux skin testing was negative to a dilution of 1:100, but a Kveim test was strongly positive, and a diagnosis of presumed sarcoidosis with lacrimal gland involvement was made.

In June 1980, because of increasing tenderness in the groin, he underwent excision biopsy of a lymph node. This showed 'foci of epithelioid cells and Langhan's giant cells, with no evidence of acid fast bacilli, consistent with sarcoidosis.' In the absence of pulmonary infiltration the patient was followed up without treatment.

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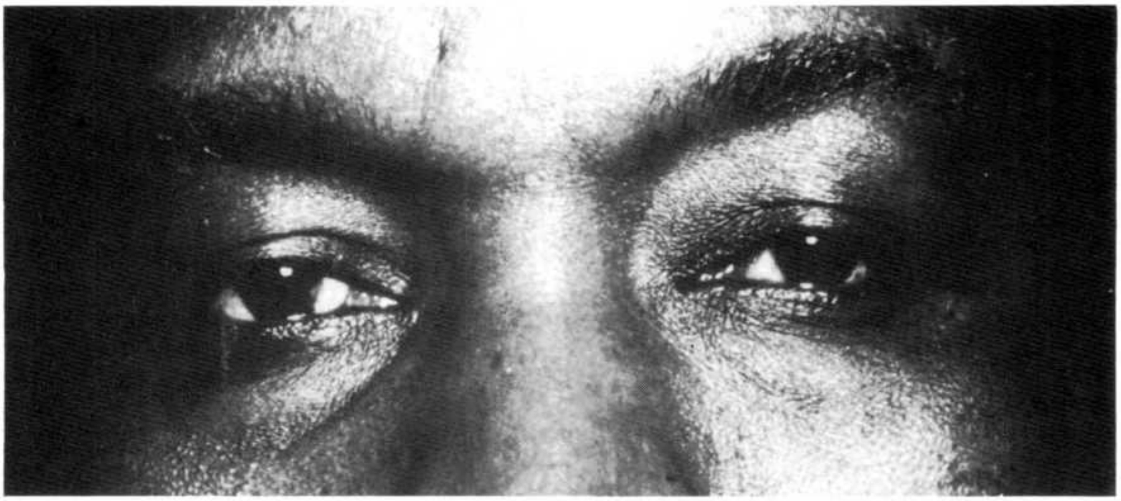

Fig. 1 *Face photograph of the patient showing enlargement of the left lacrimal gland.*

Eight months later the patient complained of redness of the left eye. On examination there was an area of fleshy episcleritis over the distal portion of the medial rectus muscle, with prominent vessels over a mass which seemed to be lying on or in the muscle belly (Fig. 2). Ocular movements were full and there was no diplopia. The lacrimal gland swelling was unchanged. Orbital CT scans (Figs. 3, 4) showed thickening of the left medial rectus muscle and lacrimal gland on axial CT scans (Fig. 3) and marked infiltration of the insertions of the other recti and Tenon's capsule on coronal scans. Because of these

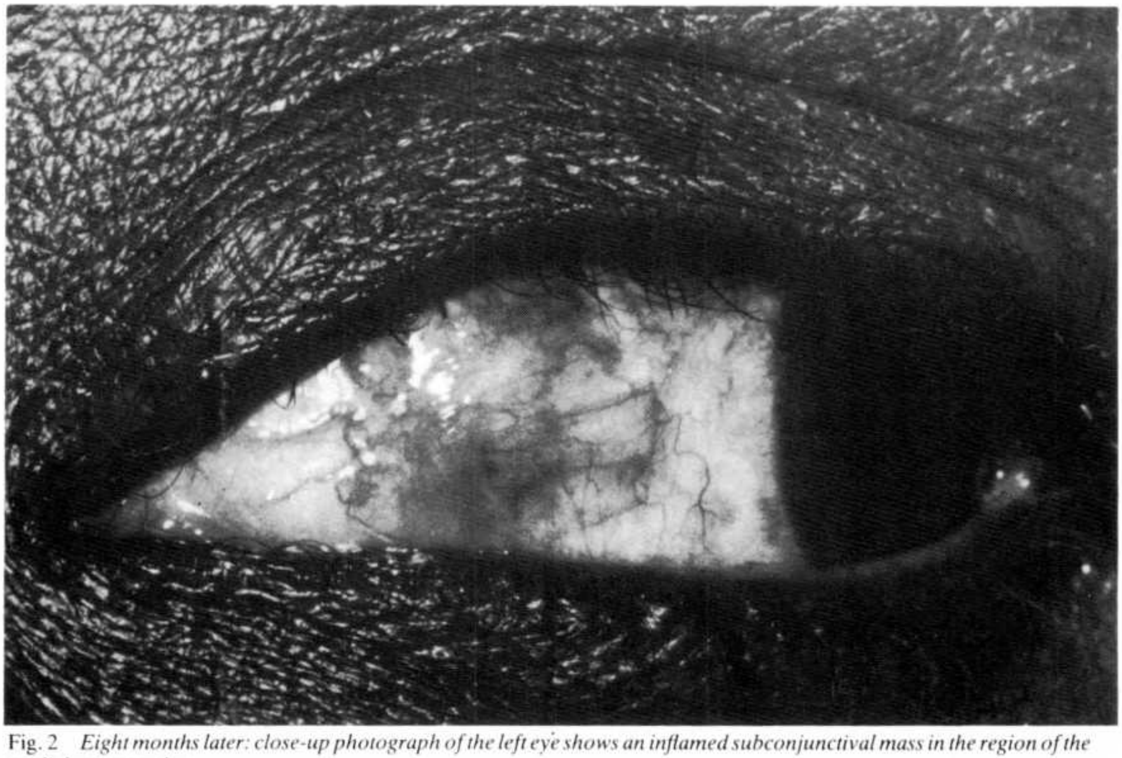

Fig. 2 *Eight months later: close-up photograph of the left eye shows an inflamed subconjunctival mass in the region of the medial rectus tendon.*

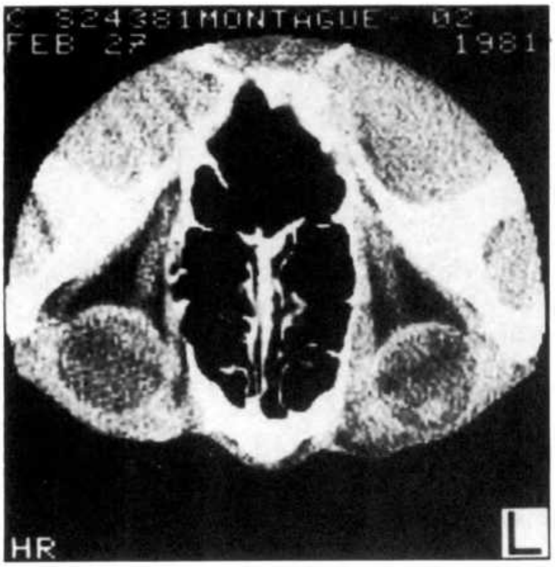

Fig. 3 *Enhanced axial CT scan shows thickening of left medial rectus muscle and swelling at its insertion with enhancement of the Tenon's capsule in each eye and prominence of the lacrimal gland.*

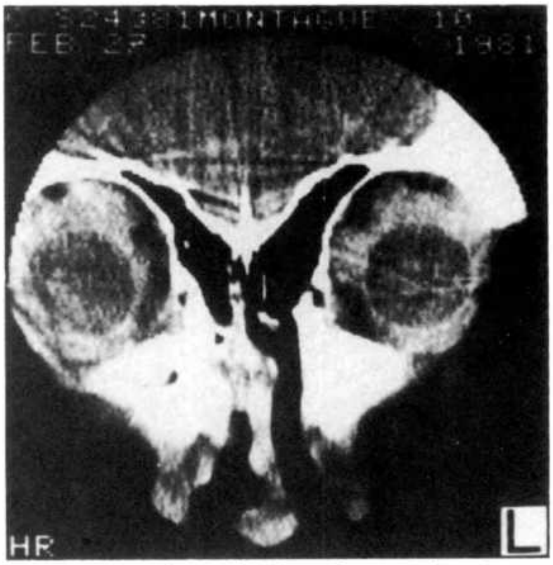

Fig. 4 *Enhanced coronal CT scan shows an enhancing circumferential infiltration of Tenon's capsule surrounding the globe with thickening of the recti tendons.*

unusual features the patient underwent in March 1981 a transcutaneous biopsy of the left lacrimal gland swelling and exploration of the medial rectus muscle. The conjunctiva was reflected to reveal a grossly thickened muscle belly (Fig. 5) infiltrated by a firm pearly white mass, from which a specimen was taken for biopsy. Histologically the lacrimal gland showed multiple, non-caseating granulomata with epithelioid cells and Langhan's giant cells (Fig. 6). There was no sign of acid fast bacilli. Similarly, the muscle biopsy showed typical sarcoid granulomata, surrounded by degenerate muscle fibres (Fig. 7). The patient made an uneventful recovery.

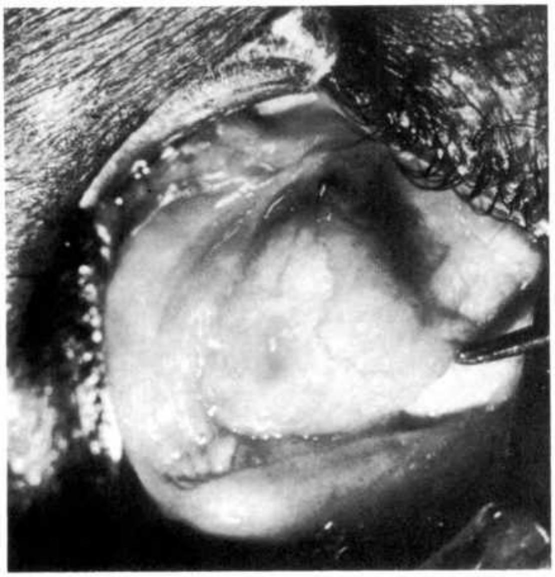

Fig. 5 *Surgical photograph showing left medial rectus tendon lying over a squint hook. The tendon is thickened and infiltrated with pearly white tissue.*

On the biopsy results and clinical findings a diagnosis of multisystem sarcoidosis was made. He was successfully treated with a course of systemic steroids, which was gradually tapered off over a few months. He has since been lost to follow-up.

Discussion

The diagnosis of sarcoidosis in this patient is substantiated by the demonstration of pathological changes in the lymph nodes, lacrimal gland, and ocular muscle, and appropriate radiological signs on the chest *x*-ray, with a positive Kveim test. Uveitis is the most common ocular manifestation of sarcoidosis and is usually seen as an anterior uveitis. But posterior uveitis is common; it may occur in the absence of anterior uveitis and is the most frequent cause of visual morbidity.[7] Involvement of the ocular adnexa from sarcoidosis is usually restricted to infiltration of the skin, conjunctivae, or lacrimal glands with granulomatous tissue. These sites are well recognised and provide good material for biopsy and histological confirmation of the diagnosis; 'blind' biopsy of apparently normal conjunctiva can be a

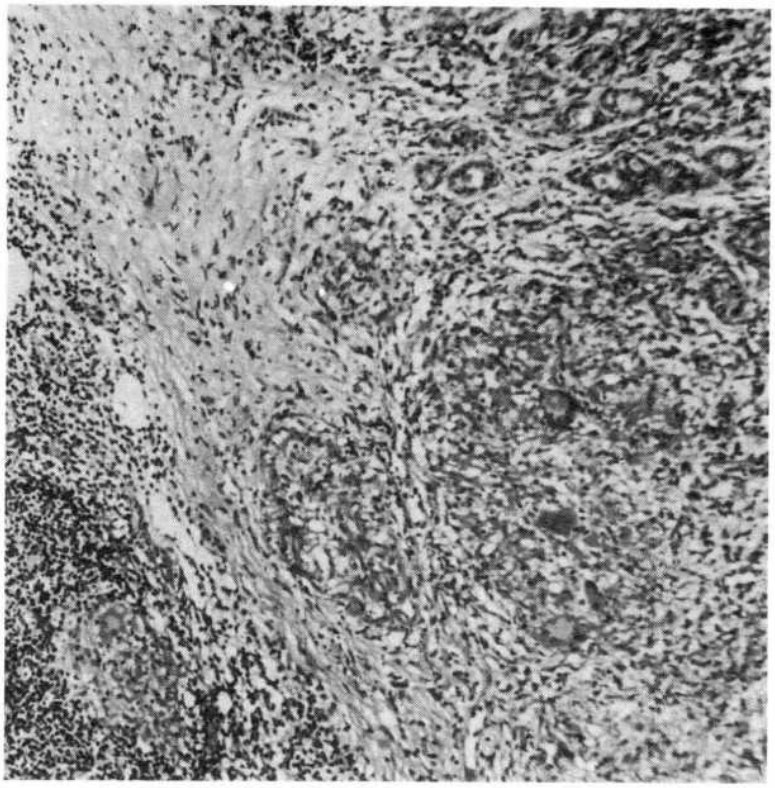

Fig. 6 *Left lacrimal gland biopsy showing a typical sarcoidal granuloma with giant cells. (Haematoxylin and eosin.)*

helpful diagnostic procedure.[8] A lacrimal gland is involved in about 75% of patients with active acute sarcoidosis. If required, lacrimal gland biopsy should be performed transcutaneously, because a transconjunctival approach may damage the ductules of the gland and risk producing a dry eye in a disease where this is already a possibility. In contrast to these manifestations sarcoidosis of the retrobulbar space is

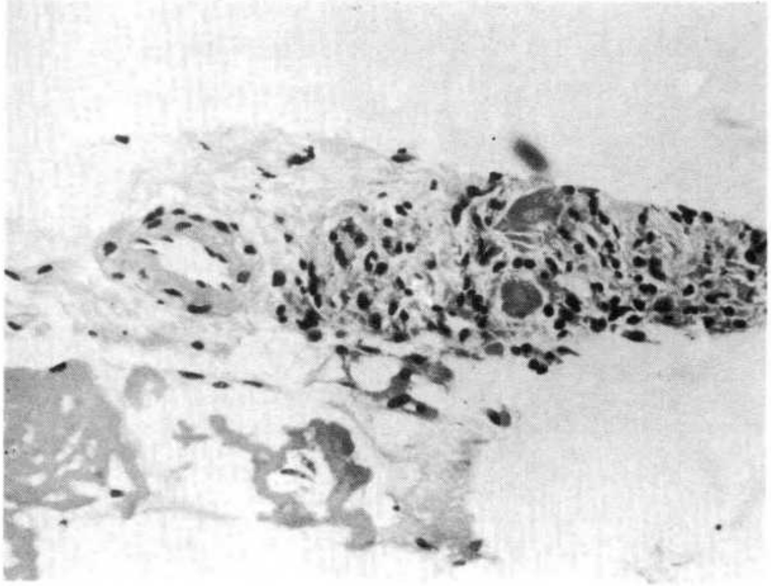

Fig. 7 *Biopsy of left medial rectus tendon shows chronic granulomatous infiltration with degenerate muscle fibres. (Haematoxylin and eosin.)*

uncommon, there being only one previous report published prior to the advent of CT scanning.[9] We see an occasional superior orbital fissure or cavernous sinus syndrome from sarcoidosis in the Medical Eye Unit, but a myositis or discrete retrobulbar mass is most unusual.

This patient showed dramatic signs of involvement in the recti tendons and Tenon's capsule on his CT scans (Figs. 3, 4).

The differential diagnosis of thickening of the external ocular muscles lies between such conditions as endocrine exophthalmos, vascular congestion associated with arteriovenous fistulas, infiltration by tumours (e.g., meningioma), inflammatory myositis, and pseudotumour. The CT scan appearances are crucial in this differential diagnosis, and most of the conditions are readily identifiable. The differentiation of an inflammatory myositis from endocrine exophthalmos can be difficult, but is aided by demonstration of involvement of the muscle tendon by an inflammatory myositis in contrast to endocrine exophthalmos, where the hypertrophy is restricted to the muscle belly itself. Our patient provides an excellent demonstration of this sign. The CT scan shows gross changes in the muscle tendons and Tenon's capsule (Fig. 4), and the muscle tendon was found to be infiltrated at surgery (Fig. 5).

We have found only one previous report of orbital myositis from sarcoidosis, where this was reported as a coincidental finding in an eye enucleated for panuveitis.[10] This seems at odds with the wealth of papers reporting skeletal muscle involvement, but might be explained by the fact that sarcoidal infiltration of skeletal muscle is often asymptomatic, and perhaps external ocular muscle involvement may be commoner than is realised. Fewer than 1% of patients with sarcoidosis have symptoms of myalgia, weakness, tenderness, or wastage, and symptomatic patients tend to have chronic disease. Indeed, if patients do complain of ocular pain and myalgia against a background of active uveitis, it is likely that the true cause of discomfort might not be recognised for what it is.

We thank Mr M D Sanders, who cared for the patient and agreed to allow us to publish the findings

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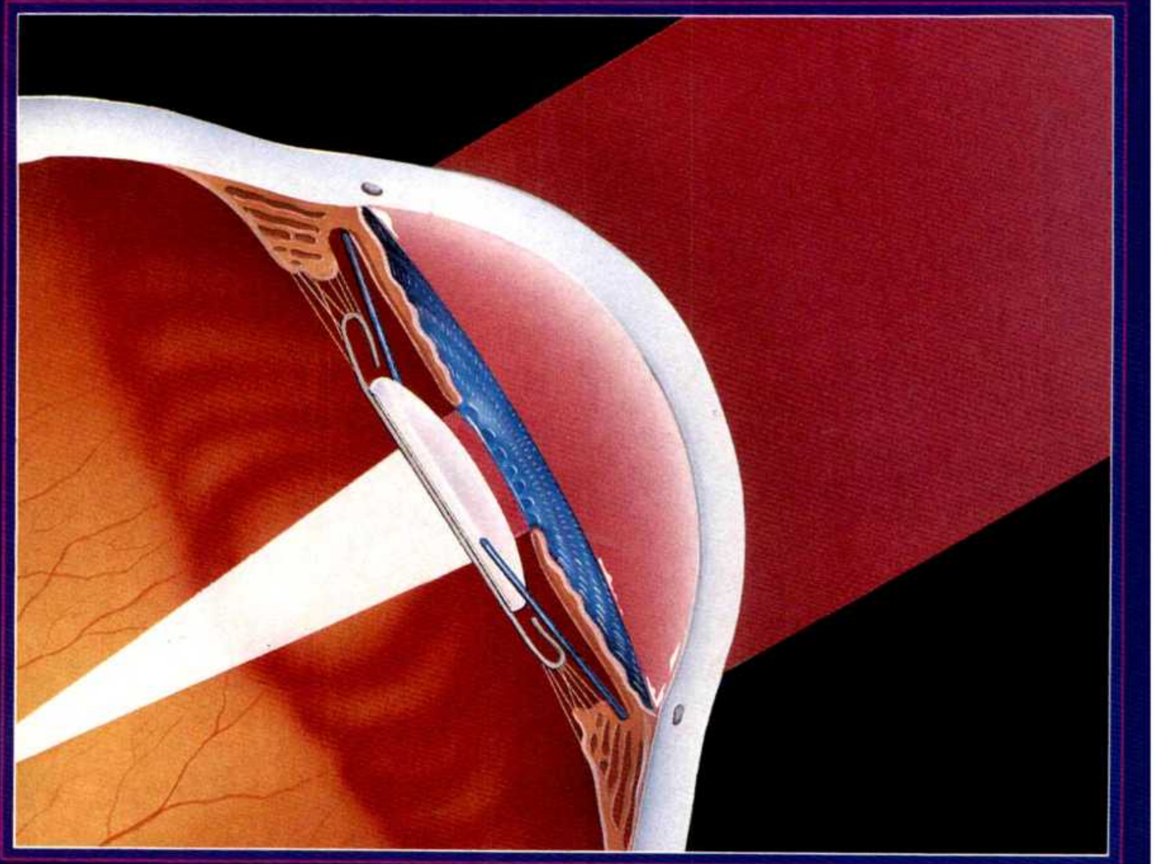

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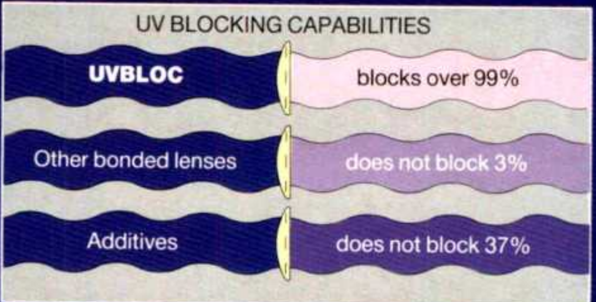

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Corneal thickness changes following cataract surgery: effect of lens implantation and sodium hyaluronate

J S H JACOB

From the West of England Eye Infirmary, Exeter

SUMMARY Consecutive patients undergoing intracapsular cataract surgery with and without lens implantation were included in one of three groups of fifteen patients for postoperative corneal thickness measurement. One group underwent cataract extraction alone, another group had cataract extraction and lens implantation using iris supported posterior chamber implants, and another group underwent lens implantation with the use of sodium hyaluronate to reform the anterior chamber after cataract extraction. Maximal increase in corneal thickness occurred within the first 24 hours of surgery in all groups. No significant difference in corneal thickness between the implant and non-implant group was found at any time. When sodium hyaluronate was used to reform the anterior chamber prior to lens implantation the increase in corneal thickness was significantly less than in the group not on sodium hyaluronate ($0{\cdot}01<p<0{\cdot}02$ on the third postoperative day). In the long term all patients' corneas returned to preoperative levels within 28 days of surgery.

Every cataract extraction even by today's microsurgical techniques involves some corneal manipulation and endothelial damage. Severe damage leads to late corneal decompensation, which has been reported as occurring in 1% of cataract extractions.[1] Interest has therefore developed in the assessment of endothelial damage either by cell counts or indirectly by measuring corneal thickness postoperatively. Miller and Dohlmann[2] recorded a significant increase in corneal thickness as long as six months after cataract extraction performed by a Graefe section. A 15% increase on the second day, with a 9% increase on the sixth postoperative day, was reported by Norn.[3] An 11·6% increase at four days with a return to normal within two weeks was reported by Wood and Maumanee.[4] Lens implantation was shown[5] further to increase corneal thickness in a series using Binkhorst iris fixated anterior chamber lenses. The average corneal thickness in this series increased during the third to fifth postoperative day to 21·7%. Similarly, Cheung *et al.*[6] found a significantly greater increase in corneal thickness on the fifth postoperative day in eyes with Federov or Binkhorst implant than in non-implanted eyes. A good correlation between endothelial cell loss measured by specular microscopy and early postoperative increase in corneal thickness was found in these patients. Miller and Stegman, using sodium hyaluronate to protect the endothelium prior to lens implantation, found a reduction in increase of corneal thickness.[7]

This study was undertaken to assess three aspects: (1) to measure the very early changes of corneal thickness following cataract extraction and cataract extraction plus lens implantation; (2) to compare thickness changes in a group without implant with those in a group of patients implanted with the modern generation of iris supported postchamber lens; (3) to observe the effect on corneal thickness of sodium hyaluronate used in conjunction with lens implantation.

Patients and methods

Forty-five consecutive patients who satisfied the exclusion criteria and were attending the West of England Eye Infirmary for cataract surgery were included in the series. They were subdivided into three groups of 15 patients. One group underwent cataract extraction alone, one group had cataract extraction plus lens implantation, and a third group in which sodium hyaluronate was used in conjunction with lens implantation.

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EXCLUSION CRITERIA

Any patient with endothelial defect, either dystrophy or cornea guttata, or any pre-existing ocular disease other than cataract was excluded. Cases were removed from the trial if there were operative complications such as vitreous loss or endothelial contact with an implant. Patients who developed complications postoperatively such as a shallow anterior chamber with wound leakage or implant dislocation were also removed from the series.

OPERATIVE TECHNIQUE

Lens extraction was performed under general anaesthesia by microsurgical techniques. All but three cases were operated on by the author. A posterior corneal section of approximately 120° was made with either a diamond knife or razor fragment. The cornea was retracted by the assistant using Colibri forceps to grasp the upper cut edge of the corneal wound and the lens extracted with a cryoprobe without the use of alpha chymotrypsinogen. The cornea was released and the anterior chamber reformed with air. In the implant group the intraocular lens, either Little Arnott, Boberg-Ans, or Severin Lens, was inserted under the air bubble through the wound with minimal retraction of the wound edge. Implantation into the pupil was achieved by a one-movement technique, engaging the iris immediately with the lower loops, pushing down until the other loops became engaged in the iris. In the group on sodium hyaluronate this material was used to reform the anterior chamber prior to lens implantation. A peripheral iridectomy was performed in all cases and the incision closed with a continuous 10/0 monofilament nylon suture. All the remaining air was replaced by balanced salt solution at the end of the procedure. No attempt was made to remove the sodium hyaluronate from the anterior chamber in the group on sodium hyaluronate. Chloramphenicol and pilocarpine 4% drops were instilled at the end of the operation on the table.

POSTOPERATIVE REGIMEN

All patients were maintained on pilocarpine drops 2% twice daily and prednisolone drops 0·5% with neomycin 0·5% four times daily for two weeks, the dosage reducing to twice daily for one month before it was stopped.

MEASUREMENT OF CORNEAL THICKNESS

Central corneal thickness was measured with a Haag-Streit pachometer which was modified according to Mishima and Hedbys[8] to ensure accurate measurement of the same area of the cornea. The modifications (Fig. 1) were made by the University of Exeter Department of Engineering and consist of extending the metal diaphragm of the Haag-Streit pachometer by approximately twice the length of the original. At an equal distance from the rotating prism axis two 1 mm fibre optic light ends were inserted 5 mm above and below the centre of the extension. The light source for the fibre optic cable was supplied from a 12 V car bulb.

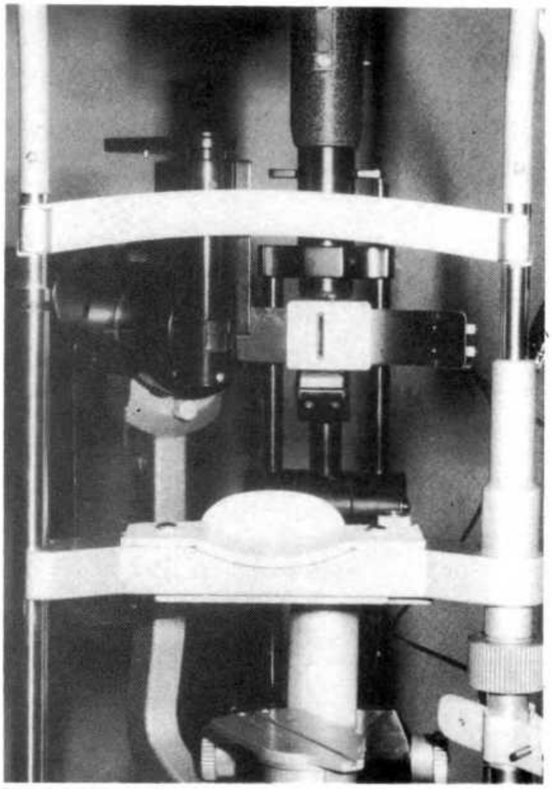

Fig. 1 *Modified Haag-Streit pachometer attached to slit-lamp.*

After the slit-lamp is adjusted for height the light beam is perpendicular to the cornea, with the patient looking straight at the slit beam when the two small lights are reflected from the corneal epithelium along the same line above and below the horizontal. The central corneal thickness is then obtained by rotating the sector shaped disc on the pachometer in the usual manner until the endothelium of the upper field is in line with the epithelium of the lower, the images of the two pinpoint lights reflected from the epithelium being kept equidistant from the horizontal line. The scale reading on the sector gives the central corneal thickness in mm. Preoperative measurements were taken on the day prior to surgery and then following surgery at 4 hours, 8 hours, 24 hours, and then every 12 hours for a total of 96 hours, when the patients were discharged from hospital. Late measurements

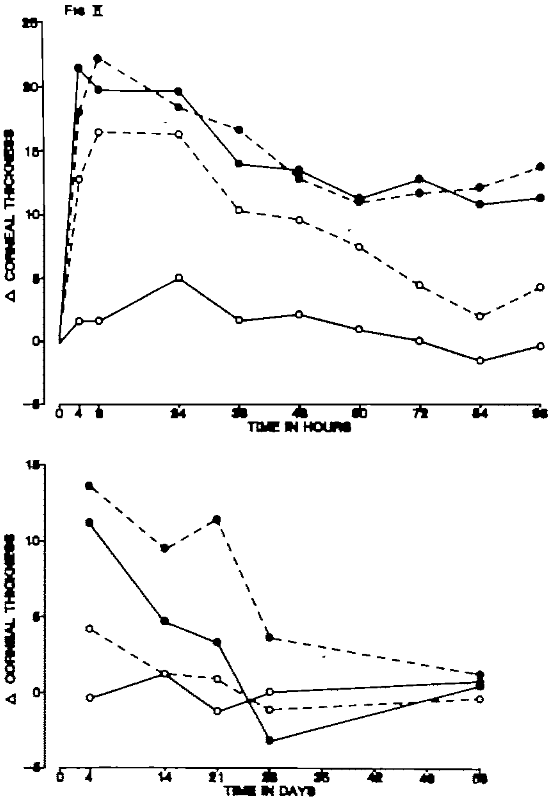

Fig. 2 *Solid circles with broken line represent the cataract extraction group plus lens implantation without sodium hyaluronate. Solid circles joined by continuous line represent plain cataract extraction without sodium hyaluronate. Open circles joined by broken line represent cataract extraction plus lens implantation with sodium hyaluronate. Open circles joined by continuous line represent control group without surgery*

were made at two weeks, three weeks, four weeks, and eight weeks postoperatively for all groups. The unoperated eye was similarly measured in 15 cases to act as control.

Results

The early and late mean percentage changes in corneal thickness are shown graphically in Fig. 2 for all groups of patients and controls. In all groups there was a return to preoperative thickness by the end of 28 days.

Plain lens extraction versus lens extraction plus lens implantation. Increase in corneal thickness in these two groups is shown in Table 1. There was no statistically significant difference between these two groups by Student's *t* test. The maximum increase in corneal thickness in both groups was seen in the first 24 hours, at 4 hours for the plain lens extraction and at 8 hours for the lens extraction with implantation. Return to preoperative thickness was slightly quicker in the plain extraction group, with only a 4·76% increase at two weeks compared with 9·5% for extraction plus implantation, though this was not statistically significant.

Lens extraction plus implantation versus lens extraction plus implantation with use of sodium hyaluronate. The increase in corneal thickness in this group is shown in Table 2. Although the mean corneal thickness was consistently less in the sodium hyaluronate group than in the group not on sodium hyaluronate group (Fig. 2), it became statistically significant only at 84 hours ($0{\cdot}01<p<0{\cdot}02$).

Discussion

Comparisons between corneal thickness and endothelial damage by means of specular microscopy have in the past shown a good correlation between the increased cell loss and early postoperative increase in corneal thickness.[4] Measurement of corneal thickness is a more readily available method and may in some ways be a better overall indicator of endothelial cell damage than counting endothelial cells over a very small area of the cornea. In this series damage to the endothelium resulted in maximal corneal oedema at 4 hours postoperatively in the plain extraction, at 8 hours postoperatively in extraction with implantation, and at 24 hours postoperatively with the use of sodium hyaluronate for endothelial protection. A peak in corneal thickness at 24 hours has been noted previously, but measurements prior to 24 hours have not been recorded by other workers. The peak increase within 24 hours may account for the clinical appearance of slight shallowing of the anterior chamber on the second and third postoperative days, when a reduction in corneal oedema leads to slight wound leakage. The maximum increase in corneal thickness of between 22·2% and 16·5% within 24 hours may be compared with other known recent series—21·7%[5] at third to fifth day[5] and 27·8% at 24 hours.[6]

In the present series no statistical significance in corneal thickness was found between the implant and non-implant groups. However, previous series have shown differences between lens implant and non-implant groups. But the present series is different from the others in that the newer generation of posterior chamber iris-supported lenses are used and cases with endothelial contact were excluded. It indicates that with modern techniques and careful surgery endothelial damage can be minimised to approach that of plain lens extraction.

In Miller and Dohlmann's series[2] 76% of the

Table 1 *Mean corneal thickness measurements (μm) for plain cataract extraction and extraction plus implantation*

Time (h)	*Preop.*	*4*	*8*	*24*	*36*	*48*	*60*	*72*	*84*	*96*
Plain extraction	479	581	573	577	576	543	530	540	530	536
Extraction + implant	454	535	554	537	529	512	504	504	506	590
		2 Weeks			4 Weeks		8 Weeks			
Plain extraction		501			494		482			
Extraction + implant		497			470		459			

Table 2 *Mean corneal thickness measurements (μm) for cataract extraction plus implantation and extraction with lens implant under sodium hyaluronate*

Time (h)	*Preop*	*4*	*8*	*24*	*36*	*48*	*60*	*72*	*84*	*96*
Extraction + implant	454	535	554	537	512	504	504	504	506	509
Extraction + implant + Na hyaluronate	474	534	532	551	523	513	590	495	483	494
		2 Weeks			4 Weeks		8 Weeks			
Extraction + implant		497			470		459			
Extraction + implant + Na hyaluronate		479			468		472			

patients still had thickened corneas at six months after operation by a Graefe section with broad iridectomy. Recent series have shown a more rapid return to normal within six months to three weeks.[5 6] In the present series there was return to normal limits within 28 days.

Sodium hyaluronate is a large polymer of repeating disaccharide units of N-acetyl glucosamide and sodium glucosonate which is becoming increasingly used to protect the cornea during lens implantation and other intraocular procedures. Miller and Stegman[7] using Binkhorst implants found that with sodium hyaluronate to reform the anterior chamber prior to lens implantation corneal thickness after surgery was significantly reduced. They also found that an 18% loss of endothelial cells compares well with that seen in non-implant eyes. Pope and Balazs,[10] however, found no significant difference in corneal thickness if the sodium hyaluronate was used to reform the anterior chamber following cataract extraction, but there was a significant reduction in corneal thickness if it was used to protect the endothelium prior to cataract extraction. In this series the use of sodium hyaluronate following cataract delivery caused a significant reduction in corneal thickness when compared with the group not on sodium hyaluronate. This difference became statistically significant at the 84-hour measurement.

Why the difference should be maximal at 84 hours is difficult to say. It may indicate the time period required for recovery of function of damaged rather than destroyed endothelial cells. The sodium hyaluronate may enhance endothelial cell recovery in some way, perhaps by diminishing the amount of prostaglandin released at the time of cell damage and so preventing further loss of cell function.

The clinical significance of increased corneal thickness in the medium term may not be very great, as in all cases the cornea returned to normal preoperative thickness within 28 days. However, changes in corneal thickness in the immediate postoperative period are an important indicator of surgical technique and corneal endothelial damage. Anything which helps to reduce endothelial damage in the short term must have some clinical benefit in the very long term.

CONCLUSION

Operative endothelial damage can be assessed by measuring corneal thickness. The maximum increase in thickness occurs within 24 hours. With modern implants, microsurgical techniques, and careful surgery no significant difference between plain intracapsular cataract extraction and intracapsular extraction plus lens implantation was found in this series. A statistically significant difference was shown in corneal thickness when patients on intracapsular lens extraction or lens implant with protection of the endothelium by means of sodium hyaluronate were compared with a group in which sodium hyaluronate was not used.

I thank Mr W Rich, Mr J Thomsitt, the late Mr F C Schwerdt and Mr G Cantrell for allowing me to use their patients in this study. My thanks particularly to Mr W Rich for his encouragement and help in reading the manuscript, to Mr M Hedgley for secretarial assistance, and the Photographic Department, Royal Devon and Exeter Hospital for the illustrations

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Hyaluronate increases intraocular pressure when used in cataract extraction

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SUMMARY A prospective randomised study of 26 eyes (24 patients) following uncomplicated intracapsular cataract surgery was carried out with three groups in which different agents were used to re-form the anterior chamber: air, seven eyes; sodium hyaluronate, seven eyes; and a combination of hyaluronate plus systemic acetazolamide, 12 eyes. The intraocular pressure (IOP) was measured by Goldmann applanation tonometry 16 hours before surgery and every eight hours after surgery for 72 hours. The IOP doubled in the two hyaluronate-treated groups for the first day following cataract surgery. By contrast, the IOP in the group receiving air initially decreased slightly. Throughout the study the effect of using acetazolamide was never statistically significant. After the first day and a half the differences in IOP among the three treatment groups disappeared, and the pressures returned to their preoperative values.

Healon is a highly purified, high molecular weight fraction of sodium hyaluronate.[1] There is evidence that hyaluronate protects the corneal endothelium during anterior segment surgery, and the agent is in wide use.[2-4] While some investigators have found it to be associated with increased IOP,[5-7] others have found it not or only rarely to be so.[8-10] We report the results of a prospective randomised study of patients undergoing cataract surgery with and without the use of hyaluronate and a third group with hyaluronate plus acetazolamide.

Patients and methods

Routine uncomplicated intracapsular cataract surgery was performed on 26 eyes of 24 patients by four surgical residents between September 1980 and February 1981. The patients were the first 24 consecutive ones without a past or family history of glaucoma, inflammatory ocular disease, or preoperative intraocular pressure (IOP) greater than 20 mmHg. The assignment to the three groups was random except for six patients receiving intraocular lens implantation, who were all treated with hyaluronate plus acetazolamide. Any patient receiving medication necessary for other medical purposes was maintained on that therapy throughout the study or excluded because of possible pharmacological effects on IOP (e.g., corticosteroids, propranolol, etc.). All patients received retrobulbar anaesthesia followed by digital compression of the globe. A fornix-based conjunctival flap was made, followed by a step incision. After peripheral iridectomy, cryoextraction of the lens was performed with the aid of 1 ml of 1:5000 dilution of alpha-chymotrypsin. The two hyaluronate-treated groups received 0·1 ml of Healon to re-form the anterior chamber prior to closure with interrupted 10-0 nylon. Air was used to re-form the anterior chamber in the third group. All intraocular lenses were of the 4-loop, iris fixation type (Intermedics) and were coated with Healon prior to insertion.

The IOPs were determined by Goldmann applanation tonometry about 16 hours before surgery, approximately eight hours (7·1±1·8, mean±SD) postoperatively, and every eight hours thereafter for 72 hours. Each patient's preoperative IOP was used as his or her own control value.

Several statistical analyses were performed on the IOP data. A two-tailed Student's *t* test was done on

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the mean difference between each IOP after surgery and its preoperative control. These means were also compared in pairs by the *t* test. In addition analysis of variance was performed on these means for all three groups at each time. To test the variation in the ratio of males to females in the three treatment groups, χ^2 analysis was performed. In both the analysis of variance and the *t* test used to compare the means from different groups the variances of the means were tested for homogeneity by Levene's test for equal variance. Except when these variances differed ($p<0{\cdot}01$), the variances within groups were obtained from the pooled data. This could be done in all *t* tests comparing hyaluronate with and without acetazolamide and throughout the analysis of variance. A p value of 0·01 was used for statistical significance.

Results

The preoperative values for the three treatment groups are given in Table 1. There was no statistically significant difference between their age, sex, and IOP.

In one of the patients who had both eyes operated on, the two eyes were randomly distributed to different treatment groups. In this patient the IOP was dramatically raised in the eye receiving hyaluronate but was decreased somewhat in the fellow eye receiving air (Fig. 1). The preoperative control data points shown at time zero were measured 16 hours preoperatively and were used as a constant.

In both the hyaluronate and hyaluronate plus acetazolamide groups the mean difference in IOP from preoperative values was significantly raised during the first two days postoperatively (Table 2 and Fig. 2). The increase was greatest around 16 hours and almost doubled the IOP during the first postoperative day. Thereafter a gradual decline was seen, with no statistical significance after about a day and a half. In the group receiving air an initial decrease in this mean IOP difference was seen at eight hours. Thereafter this difference was no longer significant. A comparison of the mean differences with and without acetazolamide (*t* test) indicated no effect of the acetazolamide ($p>0{\cdot}2$). After about the first day and a half there was no statistically significant IOP difference among any of the groups (analysis of variance) or between them and their preoperative control values (paired *t* test).

Table 1 *Preoperative control values for the three treatment groups*

	Group		
	Air	*Hyaluronate*	*Hyaluronate and acetazolamide*
Number of eyes	7	7	12
Mean patient age (years±SD)	59·9±10·9	65·4±11·1	66·8±9·5
Male/female	2/5	3/4	7/5
Intraocular pressure (mmHg±SD)	16·7±1·9	17·3±1·9	16·0±2·3

Of the 12 patients receiving hyaluronate and acetazolamide six received intraocular lenses coated with Healon and six received routine, uncomplicated intracapsular cataract extraction. These two groups were not statistically different and their data were therefore pooled. This finding is in agreement with previous studies.[11]

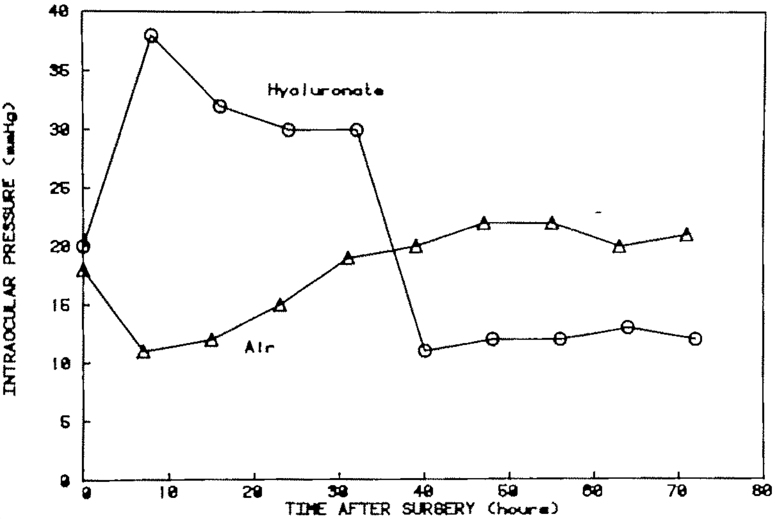


Fig. 1 *The IOP in two eyes of the same patient. Cataracts were extracted from both eyes of this patient but they were placed in separate treatment groups. The anterior chamber of one eye was re-formed with hyaluronate and the fellow eye with air. The preoperative control IOP was actually measured 16 hours before surgery*

Table 2 *Mean difference between the intraocular pressure and its preoperative control value (mmHg±SE)*

Time after anterior chamber re-formed (hours)	*Air*	*Hyaluronate*	*Hyaluronate and acetazolamide*
8	−6·6±0·8*	14·9±2 4*	15·3±2·6*
16	−2·0±2 1	16·7±1·1*	16·8±2·5*
24	−0·1±1·8	13·1±1·8*	12·6±2·7*
32	1 4±1·4	11 9±2·1*	7·9±2·3*
40	2·3±1·5	7 1±3·6	5·8±2·1
48	3·3±1·6	4·6±3 1	4·5±2·1
56	4 0±1·5	2·6±2·4	2·8±1·7
64	3 7±1·5	1·7±2 0	2·0±1·5
72	3 6±1 1	0·7±1 9	1 7±1·5
Day 1 mean	−2 9±1·4	14·9±1·2*	14·9±2·5*
Day 2 mean	1·7±1·5	9·2±2 5*	7·9±2·1*
Day 3 mean	3 6±1·4	2·4±2·3	3 0±1·6

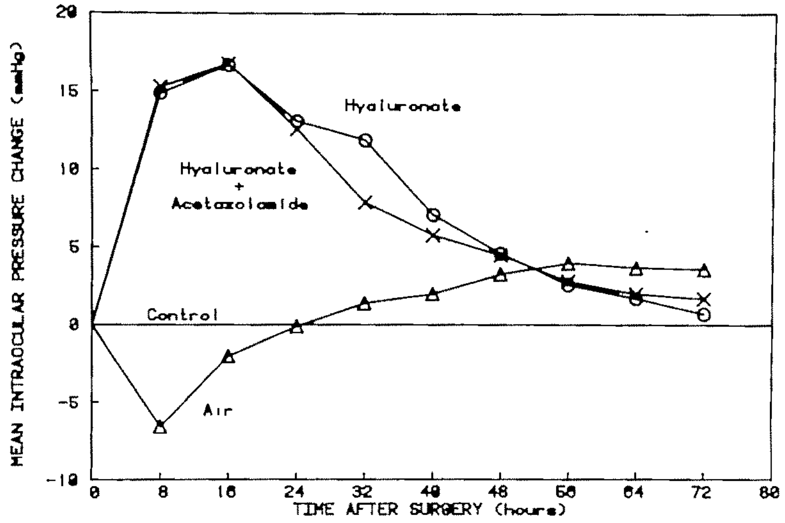
*p<0·01 from a Student's two-tailed *t* test of the average difference between the IOP before and after surgery when compared with no change (i e , 0 0±0·0). This is a paired *t* test.

Discussion

Patients receiving sodium hyaluronate had a marked ocular hypertensive response during the first day and a half postoperatively when compared with preoperative values (Figs. 1 and 2 and Table 2). The maximum IOP occurred around 16 hours postoperatively. In a hyaluronate study using rabbits and cynomolgus monkeys the IOP was shown to peak at approximately three hours,[12] probably reflecting species, age, or experimental differences. The aetiology of the ocular hypertension probably involves the large molecules of hyaluronate creating mechanical resistance in the trabecular meshwork. In a study of enucleated human eyes hyaluronate was found to cause a marked decrease in outflow facility.[13] Hyaluronidase is normally present in the anterior segment,[14] but it appears to have only a negligible role because of the large amount of hyaluronate forced into the trabecular meshwork.

Ocular hypertension associated with cataract surgery is well documented.[15-16] Kirsch[15] found the incidence of increased IOP (Schiotz >24·4 mmHg) in 72·5% of patients undergoing intracapsular cataract surgery with alpha-chymotrypsin (as used in the present study) compared with only 23·6% of patients not receiving the enzyme. The course of the 'enzyme' glaucoma was described typically from days 2 to 5 with recovery by day 7. Actual clogging of the trabecular meshwork with zonular fragments has been reported in eyes treated with alpha-chymotrypsin.[16] Extracapsular cataract extraction may be accompanied by lens debris in the anterior chamber, which may mix with hyaluronate and cause ocular hypertension. Our current method of cataract surgery is an extracapsular extraction with insertion of a posterior chamber lens. It is our clinical impression that postoperative intraocular pressures are higher than we previously observed following intracapsular cataract surgery. Even in patients receiving only saline (i.e., receiving neither alpha-chymotrypsin nor hyaluronate) ocular hypertension was observed as early as six hours after cataract surgery.[17] This has also been observed by others, with IOPs reported to be greater than 30 mmHg.[18] Implicated mechanisms include swelling of the trabecular meshwork and breakdown of the blood-aqueous barrier.[19 20] These reactions would suggest that the usually observed ocular hypertension follow-

Fig. 2 *Mean difference between the IOP at each time after surgery and its preoperative control value for the air (triangles), hyaluronate (circles), and hyaluronate plus acetazolamide (Xs) groups. The SE for each point is given in Table 2.*



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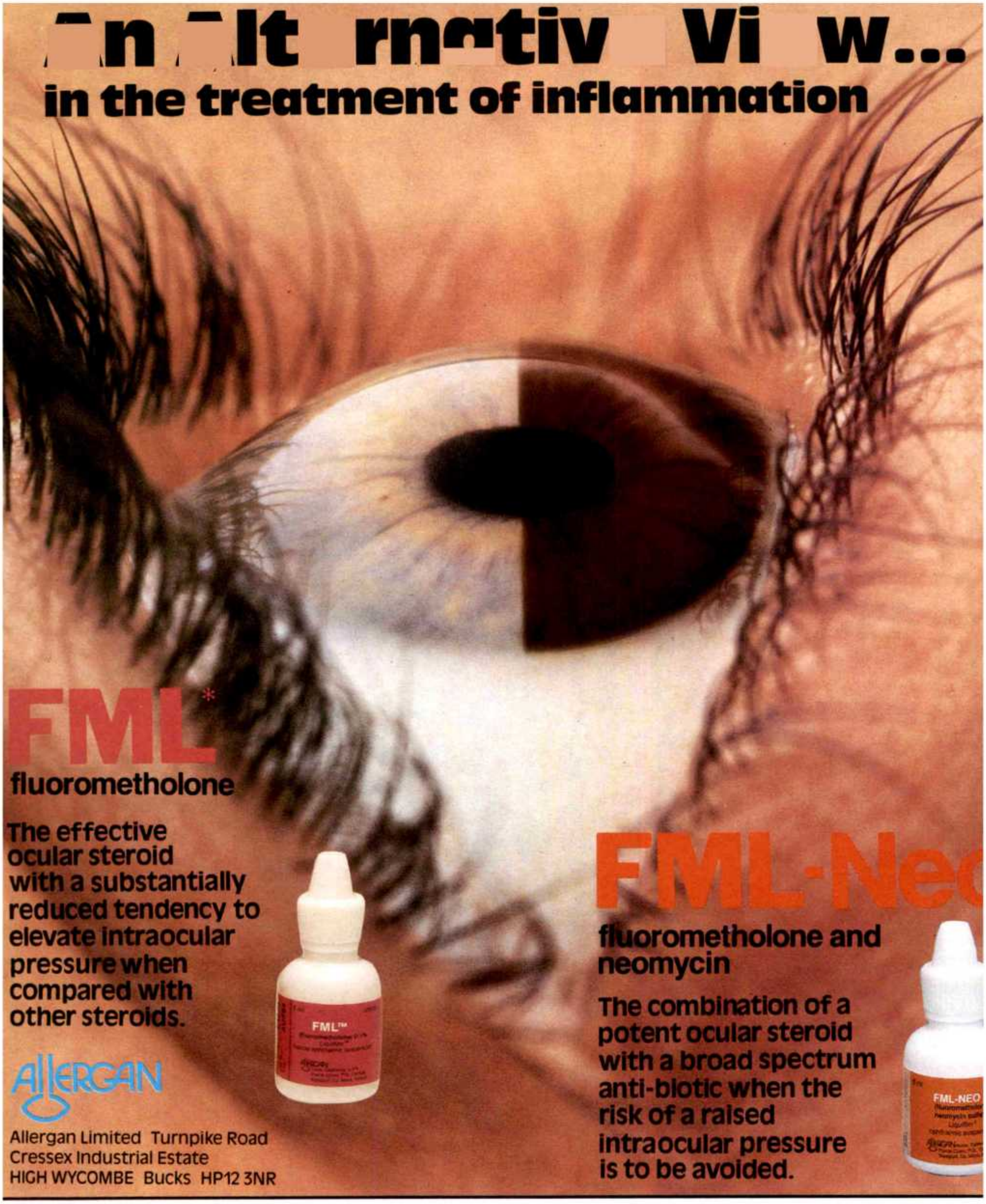

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Presentation White, microfine, sterile ophthalmic suspension containing fluorometholone (0.1%). **Uses** Topical ophthalmic suspension for steroid responsive inflammation of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe. **Dosage and Administration** 1 to 2 drops instilled into the conjunctival sac two to four times daily. During the initial 24 to 48 hours the dosage may be safely increased to 2 drops every hour. Care should be taken not to discontinue therapy prematurely. **Contra-indications, Warnings, etc.** CONTRA-INDICATIONS: Acute superficial herpes simplex keratitis. Fungal diseases of ocular structures. Vaccinia, varicella and most other viral diseases of the cornea and conjunctiva. Tuberculosis of the eye. Hypersensitivity to the constituents of this medication. **Warnings** Steroid medication in the treatment of herpes simplex keratitis (involving the stroma) requires great caution; frequent slit-lamp microscopy is mandatory. Prolonged use may result in glaucoma, damage to the optic nerve, defects in visual acuity and fields of vision, posterior subcapsular cataract formation, or may aid in the establishment of secondary ocular infections from fungi or viruses liberated from ocular tissue. In those diseases causing thinning of the cornea or sclera, perforation has been known to occur with use of topical steroids. Safety and effectiveness have not been demonstrated in children of the age group two years or below. This preparation contains benzalkonium chloride and should be used with caution in association with hydrophilic contact lenses. **Use in Pregnancy** Safety of the use of topical steroids during pregnancy has not been established. **Precautions** As fungal infections of the cornea are particularly prone to develop coincidentally with long-term steroid applications, fungus invasion must be suspected in any persistent corneal ulceration where a steroid has been used or is in use. Intra-ocular pressure should be checked frequently. **Adverse Reactions** Glaucoma with optic nerve damage, visual acuity or field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens liberated from ocular tissues, perforation of the globe. Local side-effects of steroid therapy ie skin atrophy, striae and telangiectasia, are especially likely to affect facial skin. **Pharmaceutical Precautions** Protect from freezing. **Legal Category** POM. **Package Quantities** Supplied in plastic dropper bottles of 5ml and 10ml. Basic NHS cost (as at July 1984) 5ml £1.78, 10ml £2.83. PL 0426/0028. Full prescribing information is available on request.

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Presentation Sterile, white, microfine ophthalmic suspension containing fluorometholone, NF0.1% and neomycin sulpha BP0.5% (equivalent to 0.35% neomycin base). **Uses** FML-NEO* is indicated for the management of steroid responsive inflam the palpebral or bulbar conjunctiva, cornea and anterior segment of the globe, when threatened or complicated by infect neomycin-sensitive organisms. **Dosage and Administration** One or two drops in the conjunctival sac two to four times c During the initial 24 to 48 hours, the dosage may be safely increased to one drop every hour. Care should be taken not to c treatment prematurely. Shake well before using. **Contra-indications, Warnings etc.** Acute untreated purulent ocular inf Acute superficial herpes simplex (dendritic keratitis), vaccinia, varicella and most other viral diseases of the conjunctiva ar Ocular tuberculosis, fungal diseases of the eye and hypersensitivity to any of the components of the drug. **Warnings** As fc above and, in addition in diseases due to micro-organisms resistant to neomycin, infection may be masked enhanced or a the steroid. Prolonged use may result in overgrowth of nonsusceptible organisms. Articles in current medical literature i increase in the prevalence of persons sensitive to neomycin. The possibility of such a reaction should be borne in mind. If or other untoward reactions occur, discontinue the medication. **Precautions** Patients with histories of herpes simplex ke should be treated with caution. Use of topical steroids may increase intraocular pressure. Safety of intensive or protracte topical steroids during pregnancy has not been substantiated. Local side effects of steroid therapy ie skin atrophy, striae telangiectasia, are especially likely to affect facial skin. **Pharmaceutical Precautions** Shake well before using. Do not fre **Category** POM. **Package Quantities** Available in 5ml plastic dropper bottles. Basic NHS cost (as at July 1984) £1.90. PL 042(Prescribing information is available on request.

*Trade Mark

ing cataract surgery may be aggravated by the use of hyaluronate.

The present data revealed an initial, transient ocular hypotension in the patients receiving air (Figs. 1 and 2 and Table 2). This may have resulted from the direct effect of air or, possibly, from the relatively long operating times of resident surgeons who performed all the surgery. Long operating times may have caused mild choroidal detachments and hypotony. Brown *et al.*[21] measured the IOP three hours after cataract surgery in 20 eyes that had received alpha-chymotrypsin and had an air bubble left in their anterior chambers. Their results are suggestive of an early decrease in the IOP (measured at three hours postoperatively). Air, a compressible substance that is absorbed slowly over several days, may damage the endothelium, but the effect appears to be short-lived.[22] It may be that a combination of hyaluronate and air would neutralise the IOP changes, though surgical visualisation is decreased when air mixes with hyaluronate.

The unique physiochemical nature of hyaluronate probably negates the therapeutic value of agents that reduce aqueous secretion (e.g , acetazolamide). Removal of excess hyaluronate prior to closure may prove to be of value, although it did not alleviate the outflow blockage in enucleated eyes filled with hyaluronate.[13] No increase in morbidity was evident in our patients, but the potential for ischaemic retinal and optic disc disease is real. Although hyaluronate is extremely useful in intraocular surgery, we believe that further studies are important to develop appropriate treatment for the raised IOP in patients receiving it.

The patients were all operated on at the Wishard Memorial Hospital, Indianapolis, Indiana, between September 1980 and February 1981 The authors would like to thank John O'Riordan for his advice and assistance with the statistical analyses This investigation was supported in part by National Eye Institute research grant EY 04085 and a Research to Prevent Blindness research grant professorship (JTE)

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British Journal of Ophthalmology, **69**, 576–579

Postural response of intraocular pressure following traumatic hyphaema

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SUMMARY Twenty patients with previous unilateral traumatic hyphaema and 25 age-matched controls were studied. There was a progressive rise in intraocular pressure when the patient changed from the standing to the sitting position and then to the lying position in both groups. No control eye showed a rise greater than 2 mmHg when the subject changed from sitting to lying. However, 14 (70%) of the injured eyes and 12 (60%) of the fellow eyes showed an exaggerated response. We suggest that the presence of an abnormal postural response may indicate a predisposition to post-traumatic glaucoma. Our findings are compatible with a linked control of postural intraocular pressure response between the two eyes.

Abnormal postural response of the intraocular pressure has been suggested as an indicator in the detection of glaucoma[1] and also in the identification of ocular hypertensive patients at risk of developing glaucoma.[2] Traumatic hyphaema is commonly associated with damage to the anterior chamber angle,[3] and the pathological changes seen have been linked with the development of chronic secondary glaucoma.[4] We studied the abnormal postural response in an attempt to identify which patients might develop glaucoma following traumatic hyphaema.

Materials and methods

Twenty patients with unilateral traumatic hyphaema who had been admitted to Southampton Eye Hospital immediately after injury were selected from the hospital ledger. They were examined on average eight months after injury (range 5 to 36 months), and their ages were 14 to 38 years, there being 15 males and five females. The hospital routine led to topical steroids being used in most cases for the first two weeks only following discharge. No ocular therapy was being used at the time of examination. No account was taken of either the size or the duration of the hyphaema, medical illness, or drug therapy. Twenty-five control subjects were studied, all of whom were in good health and had no past ocular history. Their ages ranged from 14 to 33 years, there being 16 males and nine females. Both control subjects and patients had normal visual fields prior to investigation. The anterior chamber angle of all injured eyes was studied with a gonioscope.

All intraocular pressure measurements were taken as an average of two 10-second recordings with an Alcon applanation pneumotonograph which had been recently calibrated. The required posture was assumed for 15 minutes before each pressure measurement, and measurements were made in the following positions consecutively: sitting, lying, sitting, and standing. The right eye was always examined first.

Results

The mean intraocular pressures in the four positions are shown in Table 1. There are illustrated graphically in Fig. 1.

The intraocular pressure in the original sitting position was similar in all the eyes. The greatest postural change in intraocular pressure occurred on moving from the sitting to the lying position and is illustrated in Figs. 2, 3, and 4. No control eye had a rise greater than 2 mmHg, while 14 (70%) injured eyes and 12 (60%) fellow eyes showed a rise greater than 2 mmHg. The greatest rise was 9 mmHg in one

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*Work undertaken during fourth year medical student elective.

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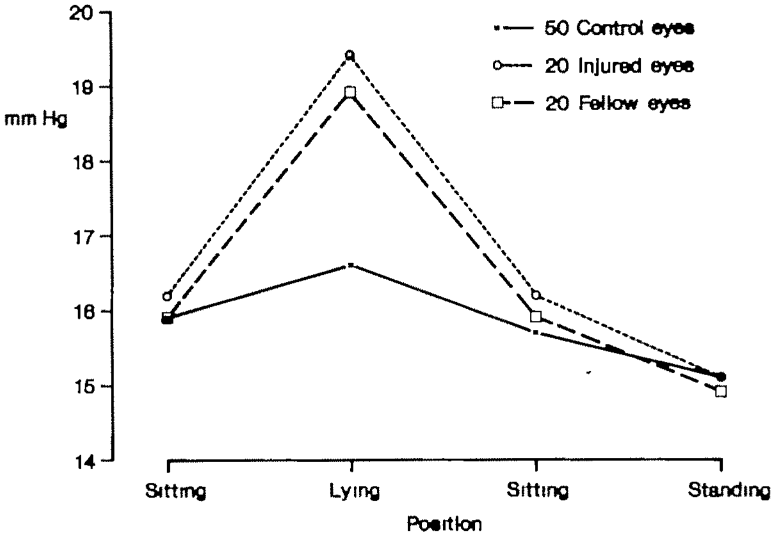

Fig. 1 *Mean intraocular pressures of control, injured, and fellow eyes in different postures.*

Table 1 *Mean (standard error) intraocular pressures in mmHg*

	Position			
	Sitting	*Lying*	*Sitting*	*Standing*
Injured eyes	16·2 (0·48)	19·4 (0 77)	16 2 (0·36)	15·1 (0 36)
Fellow eyes	15 9 (0·49)	18·9 (0·39)	15·9 (0 37)	14·9 (0·36)
Control eyes Left	15 9 (0·26)	16·7 (0·26)	15·8 (0·24)	14·9 (0·24)
Right	15 8 (0·19)	16·6 (0 19)	15·6 (0·26)	15·2 (0·21)

injured eye and 10 mmHg in one fellow eye in different patients (the contralateral eye rise being 5 mmHg and 4 mmHg respectively). Only three patients showed a rise in intraocular pressure in the fellow eye greater than the injured eye, while six injured eyes had a rise greater than the fellow eye.

There was a significant difference between the average response in a sitting position and that in a standing position (observed $F'_{1,29}=31\cdot69$, $p<0\cdot01$). This pattern of response did not differ between groups or between eyes (observed $F'_{1,29}=1\cdot02$, $p>0\cdot05$ and observed $F'_{1,72}=0\cdot68$, $p>0\cdot05$ respectively).

There was a significant difference between the average response in a sitting or standing position and that in a lying position (average sitting/standing=15·62, lying=17·76; observed $F'_{1,29}=218\cdot93$, $p<0\cdot01$). This pattern of response was significantly different between groups (observed $F'_{1,29}=66\cdot35$, $p<0\cdot01$). There was a much more pronounced rise in pressure in patients than in controls.

The pattern of response between eyes was not significantly different between groups (observed $F'_{1,72}$

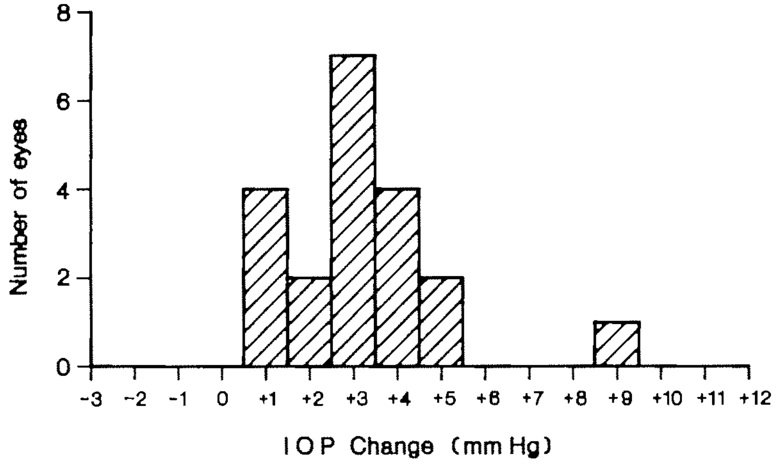

Fig. 2 *Injured eyes (20): IOPs on change from sitting to lying*

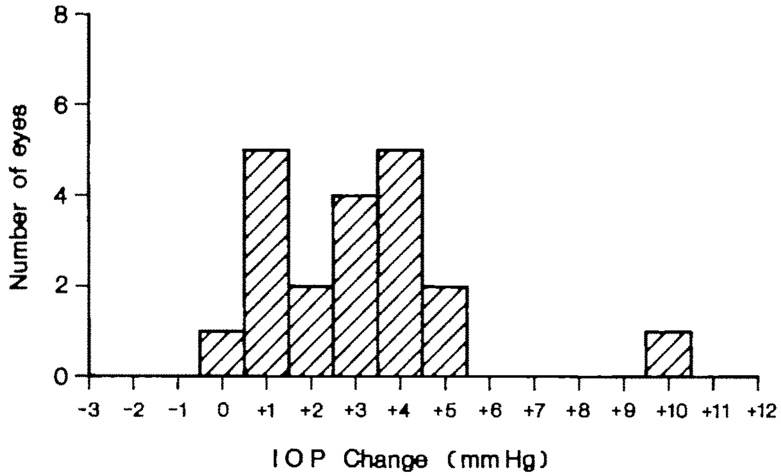

Fig. 3 *Fellow eyes (20). IOPs on change from sitting to lying*

=0·64, p>0·05). The rise in pressure was binocular, but the magnitude of this rise depended on group membership, being greater in patients than in controls.

Discussion

The usefulness of the pneumotonometer in measuring postural changes in intraocular pressure is well documented,[5-8] and our intraocular pressure values in the sitting position correspond well with previously reported figures.

Our results show a progressive rise in the intraocular pressure from standing to sitting to lying in contrast to those of Langham,[6] who showed no difference between sitting and standing values. The patients in our study showed an abnormal postural response in the injured eye and a remarkably similar response in the fellow eye. As regards the postural change from sitting to lying (which produces the largest response), 12 patients (60%) showed a rise in both eyes greater than 2 mmHg, while a further two patients had a rise greater than 2 mmHg in the injured eye only. This marked bilaterality of abnormal postural response contrasts with the bilateral abnormal response in only three out of 37 ocular hypertensive patients studied by Leonard *et al.*,[2] while Inglima[1] described four patients with unilateral glaucoma who showed an abnormal response in the affected eye only.

Anderson and Grant[8] commented on the similarity of postural intraocular pressure response in the right and left eye of patients referred with possible glaucoma. Our study confirms this in both patients and controls, irrespective of whether the response was normal or abnormal. Our results also agree with previous reports[9 10] that the abnormal postural response is not related to the level of intraocular pressure in the original sitting position.

An abnormal postural intraocular pressure response has been repeatedly demonstrated in patients with open angle glaucoma[5 6 9 11] and more recently in conditions having a well-established association with glaucoma, these being ocular hypertension,[2] retinal vein occlusion[9 10] and this study of eyes with traumatic hyphaema. Only this study and those of Williams and Peart[9 10] show that a bilateral abnormal response between an affected eye and its fellow is a frequent finding. Williams and Peart[10] considered that the explanation for this finding was a pre-existing abnormality in both eyes tending to a predisposition to retinal vein occlusion. However, we would argue from our findings that an alternative explanation is that an abnormality in one eye (whether due to central retinal vein occlusion or trauma) resets the mechanism that controls the intraocular pressure of the two eyes when the posture is changed. Welsh[12] too showed how injury to one eye, in the form of laser trabeculoplasty, affects the intraocular pressure in the contralateral eye—both intraocular pressures falling after treatment.

Characteristics of the postural response which have been demonstrated by other workers are rapidity of change to a new level of intraocular pressure[6] and the sustained maintenance of this level.[2 6] Our results also showed reproducibility, as the second reading in the sitting position corresponds well with the previous reading in this position (see Fig. 1).

Leonard *et al.*[2] suggested that local vasomotor function may be important in the pathogenesis of raised intraocular pressure when lying and that there is a complex failure of homoeostasis when the postural response is abnormal. The homoeostatic

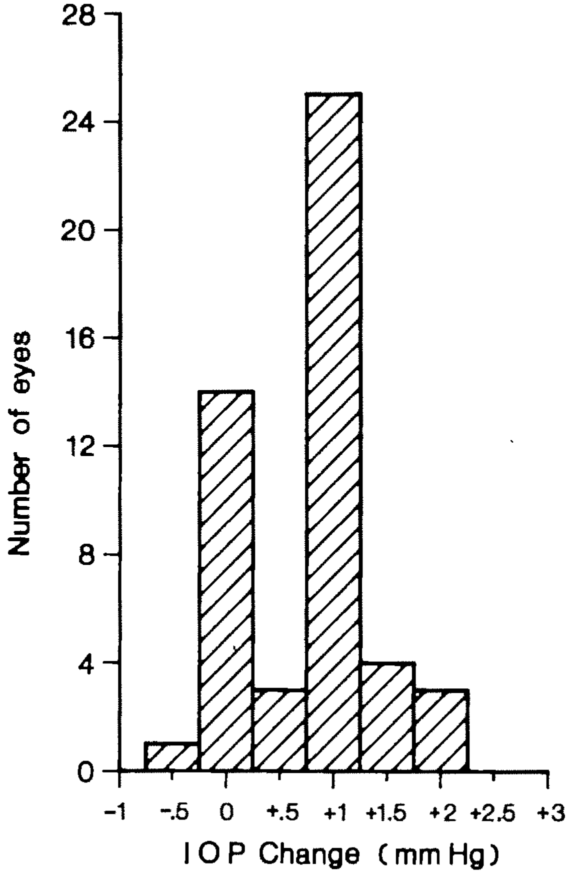

Fig. 4 *Control eyes (50): IOPs on change from sitting to lying.*

mechanism is unknown, but we conclude that a neuronal control with linkage between the two eyes is most likely to account for a bilateral, rapid, sustained, reproducible response.

Further studies are needed to assess binocular aspects of intraocular pressure control in pursuit of possible forms of linkage.

We would like to thank Mr M J Absolon, Mr I H Chisholm, Mr J I McGill, and Mr C B Walker for permission to study patients under their care

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Q fever as a possible cause of bilateral optic neuritis

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SUMMARY A 59-year-old farmer developed a bilateral optic neuritis in the course of an infection with *Coxiella burnetii* (Q fever), resulting in a lasting unilateral blindness. A complete medical (including neurological) evaluation gave no evidence of other possible causes. A possible source of infection was cattle.

Q fever is an infectious disease caused by *Coxiella burnetii*. It was supposed to be rare in the Netherlands, but recently 33 cases of Q fever have been described.[1] In one of these cases an acute infection was accompanied by an optic neuritis. Only a few cases of optic neuritis in the course of Q fever have been described in ophthalmological journals.[2-4] The following case history suggests that the bilateral optic neuritis was caused by an infection with *Coxiella burnetii*. The evidence is based on both serological and epidemiological data.

Case history

On 26 June 1983 a 59-year-old farmer consulted an ophthalmologist elsewhere with complete loss of vision of his right eye. The day before he had noticed a loss of parts of his visual field. On 13 June, two weeks before his (subjective) visual complaints, he experienced a period of fever for four days. His temperature rose to 40°C. He had no complaints related to the respiratory tract, and no headache, myalgia, nausea, or vomiting. During this period there had been urinary retention, for which he was treated by his general practitioner. He had noticed a diminished appetite for food, which lasted a few weeks. The fever was preceded by a week of general malaise and subfebrile temperatures. There was nothing of note in his previous medical history. As a farmer he had occasionally been in contact with pesticides of unknown nature.

CLINICAL INVESTIGATION

On examination on 26 June 1983 the patient had no perception of light in the right eye. Vision in the left eye was 10/10. Funduscopic examination revealed a swollen optic disc on both sides (Fig. 1). The visually evoked cortical potentials of the right eye were not recordable. The potentials of the left eye had normal amplitude and latency. Goldmann perimetry of the left eye gave normal results. Fluorescein angiography gave no additional clues to the diagnosis: on both sides there was pathological leakage of the optic disc without signs of vasculitis.

With the presumed diagnosis of bilateral optic neuritis the patient was treated with parabulbar injections of corticosteroids. At the same time he received orally vitamin B_1.

On neurological and internal examination no abnormalities could be found except a slight elevation of protein (0·69 g/l; normal 0·10–0·50 g/l) and a slight increase in the number of cells in the cerebrospinal fluid (erythrocytes 8/3 mm^3, polymorph leucocytes 1/3 mm^3, monocytes 5/3 mm^3, and lymphocytes 19/3 mm^3).

The patient was transferred to the Eye Hospital on 6 July. He still had no perception of light in the right eye. Visual acuity of the left eye was 10/10 (with S −0·50). Eye pressures with applanation tonometry were normal. Both eyes were white, and the anterior segments showed no signs of inflammation or other abnormalities. A right afferent pupillary defect was present. On funduscopy the right optic disc was pale and had blurred margins. A small haemorrhage was centrally located on the disc. The optic disc of the left eye was oedematous. At the 12 o'clock position the retinal vessels showed sheathing. Eye movements were painful, especially those of the right eye.

On 7 July the patient underwent a complete neurological examination at the Department of Neurology. No abnormalities were found. The spinal tap revealed a total protein of 0·92 g/l. Polymorpho-

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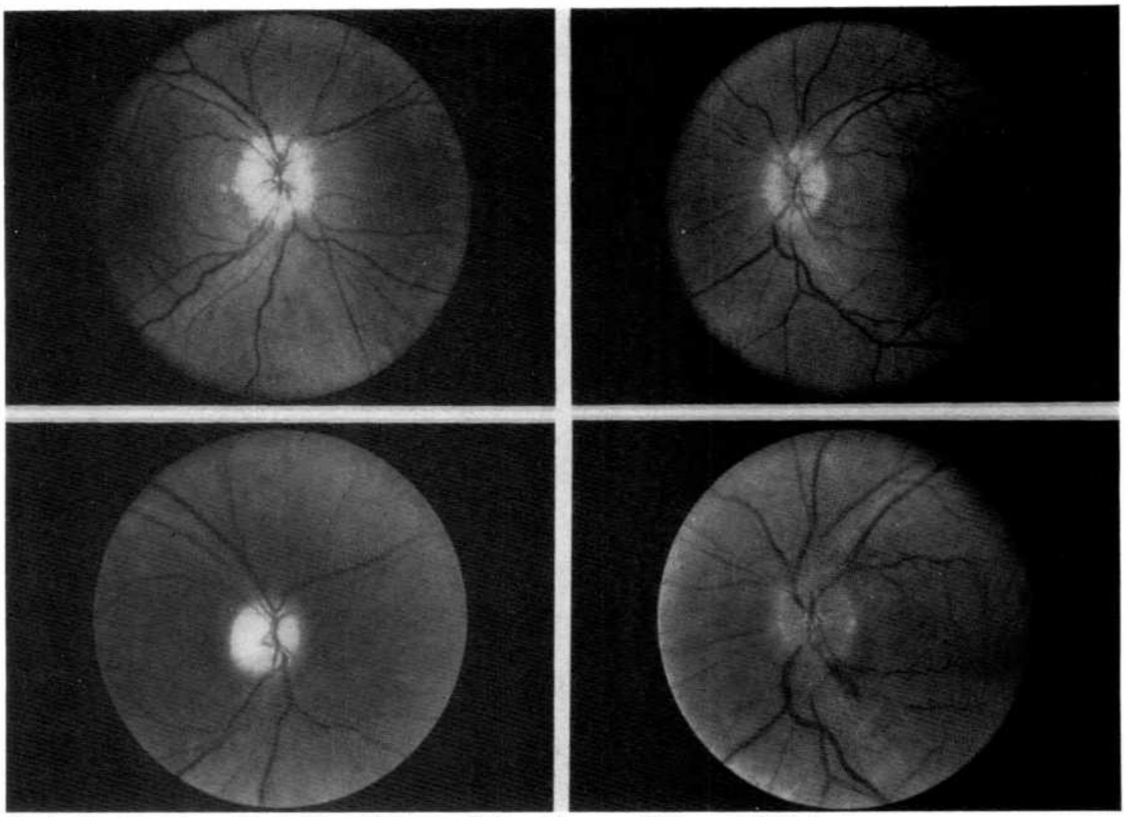

Fig. 1 *Fundus photographs of right and left eye on 26 June (above) and 3 August 1983 (below).*

nuclear leucocytes were 16/3 mm^3 and lymphocytes 63/3 mm^3. CT scan showed both optic nerves to be thickened. The presumptive diagnosis of bilateral optic neuritis was confirmed. In view of the period of fever and the cellular response in the cerebrospinal fluid a viral infection was assumed to be a possible cause of the disease. While waiting for the result of virological examinations, he was treated with a short course of dexamethasone orally.

VIROLOGY

Virological investigations were performed at the Virological Laboratory of the Public Health Service of Rotterdam. No serological evidence of an infection with *Chlamydia psittaci*, *Mycoplasma pneumoniae*, or influenza A, B, mumps, adeno-, herpes simplex, varicella zoster, or cytomegalovirus was found. A rise of the antibody titre to *Coxiella burnetii* (phase II) in the complement fixation test was found: 1:4 on 29 June 1983 and 1:16 on 11 July 1983. The titre of IgM antibodies against *C. burnetii* (immunofluorescence test) was 1:1024 on both dates. The IgG antibodies against *C. burnetii* (immunofluorescence test) rose from 1:1024 on 29 June to 1:4096 on 29 July 1983. The course of the antibody titre, shown in Fig. 2, was followed during several months. In the cerebrospinal fluid, taken 24 days after the beginning of the visual complaints, no IgM or IgG antibodies against *C. burnetii* was found. From the same sample, inoculated into guinea-pigs, no *C. burnetii* was isolated, nor did the guinea-pigs form antibodies against this organism.

EPIDEMIOLOGY

This farmer had a horse, a cow, five calves, a dog, cats, and chickens. During the first twelve days of May 1983 he had spent the night in a barn, because the horse he owned had to foal. During the winter time the other animals also stayed in this barn.

In the cow and three calves that were investigated no antibodies against *C. burnetii* could be demonstrated by means of the complement fixation test. On the farm where he usually bought his calves, however, three of 10 cows that were investigated had antibodies against *C. burnetii*. The farmer's wife had no antibodies against *C. burnetii*.

When it became known that this patient suffered from Q fever, he was treated with a daily dose of 100

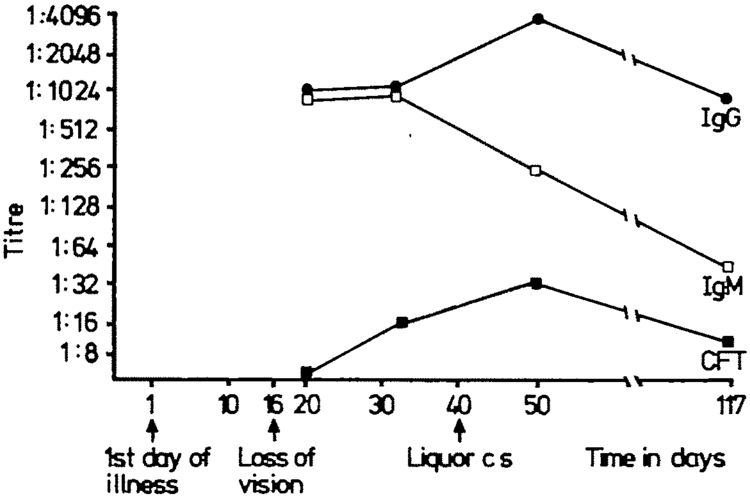

Fig 2 *Course of antibodies determined by means of a complement fixation test (CFT) and immunofluorescence test (IgG and IgM) against* C. burnetii *(phase II) in a patient with acute optic neuritis. Liquor C.S. = time at which cerebrospinal fluid was tapped*

mg doxycycline. He was discharged from hospital on 29 July. Visual acuity of his right eye had not improved. The visual acuity of his left eye remained normal. On funduscopy the findings were the same: a pale disc with blurred margins on the right side and the same degree of oedema on the left side. Medication on dismission was 2 mg dexamethasone phosphate and 100 mg doxycycline daily.

Discussion

Neurological signs in the course of Q fever are rare.[7] They vary and are non-specific for the disease. Mental confusion during the acute stage of the disease was seen in 7% out of 180 described patients in California.[8] The following defects have also been reported: neuritis with atrophy of the proximal musculature, polyradiculopathy, isolated neuritis of the cranial nerves, and meningoencephalitis.[9] The cerebrospinal fluid is usually normal, though a slight pleocytosis or increased protein content is found in some cases.[10] It should be noted that myalgia of the nuchal musculature, often seen in acute Q fever, may be confused with true meningeal irritation.

Optic neuritis has been described in only five cases.[3,4] In all these cases there were bilateral optic disc abnormalities and in at least three of them other neurological defects—encephalitis (2) and mental confusion. The patient we described had no other neurological symptoms besides the optic neuritis. The urinary retention might have been of neurological origin. From the bilaterality of the optic neuritis alone, no causal relationship can be made with the Q fever. However, there were no signs of other viral infections that could have caused a similar clinical picture (in particular, mumps, influenza, and varicella zoster). Bilateral optic disc abnormalities may also be found in disseminated sclerosis or in various intracranial diseases. Neither the history, the medical examination, nor the results of the CT scan showed any evidence of these. A bilateral ischaemic optic neuropathy caused by a temporal arteritis or diabetes mellitus was also ruled out. Serological syphilitic reactions were negative.

Isolation of the causative organism of Q fever from the cerebrospinal fluid (after inoculation in the guinea-pig or yolk sac of an embryonated chicken egg) could have given a solid proof of the genesis of the optic neuritis. Unfortunately only cerebrospinal fluid taken 24 days after the beginning of the symptoms could be investigated, and inoculation of it was negative. Nevertheless the relationship between the optic neuritis and the Q fever is made very probable by the course of the antibody titre against *C. burnetii*. At the beginning of the visual complaints the IgM titre against *C. burnetii* was 1:1024 and had reached its highest point. The IgG titre continued to rise for several more weeks. It appears that the visual loss coincided with the acute phase of the infection.

As to the aetiology of optic neuritis in Q fever two possibilities can be mentioned: a direct effect of the micro-organism on the nerve fibres or an indirect effect on the nerve fibres through a vasculitis.[11]

The serological demonstration of an infection with *C. burnetii* in the cattle of the farm from which the patient purchased his cows and calves gives us an indication of the possible source of infection. If one assumes that the patient was infected during the long stay in his barn (an environment with a potentially high infection risk from dust) an incubation period of 33±5 days can be postulated. Although incubation periods of 14 to 21 days are generally found in Q fever, periods up to 37 days have been described.[12] The farmer's wife, who had not slept in the barn, had no antibodies against *C. burnetii.*

In the treatment of Q fever doxycycline 100 mg daily or tetracycline HCL 1-2 g daily is the drug of choice. Generally speaking the prognosis is favourable. Neurological defects are usually temporary. On the other hand four out of five patients reported to have had optic neuritis had a lasting decrease in visual acuity and an optic atrophy. The same was true of our patient: one year after the onset he still had no perception of light in his right eye; his left eye retained a visual acuity of 10/10.

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Retinal detachment with proliferative vitreoretinopathy: surgical results with scleral buckling, closed vitrectomy, and intravitreous air injection

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SUMMARY Seventy-five cases of total retinal detachment complicated by the more advanced grades (grades C and D) of proliferative vitreoretinopathy were treated with scleral buckling, vitrectomy, and air-fluid exchange. The overall reattachment rate was 56%, ranging from 100% in grade C-1 to 26% in grade D-3. The postoperative visual acuity was 6/120 or better in 48% of the 42 eyes in which the retina was reattached. The major causes of surgical failure were redetachment from persistent vitreoretinal traction (32%) and intraoperative complications (12%).

Retinal detachment with fixed retinal folds and rigid transvitreous membranes is the major cause of failure after scleral buckling operation.[1] Treatment with scleral buckling,[2,3] vitrectomy,[4-6] silicone oil injection,[7-10] and other intravitreous drugs[11-13] has been described. However, it has been impossible to compare the results of these different reports because of the lack of a uniform classification system.

In 1981 the Retina Society Terminology Committee[14] proposed the term 'proliferative vitreoretinopathy' (PVR) to designate the clinical condition formerly known as 'massive vitreous retraction' (MVR), 'massive preretinal retraction' (MPR),[15] 'massive periretinal proliferation' (MPP),[4] or 'massive preretinal fibroplasia' (MPF).[16] PVR was classified into grades of severity.[14] Grade A (minimal) is characterised by pigment clumps and vitreous haze, both findings not unique to PVR. Grade B (moderate) has surface wrinkling of the retina, rolled edges of retinal breaks, and subtle preretinal membranes. Grade C (marked) with full-thickness retinal folds is subdivided into C-1, C-2, and C-3, with fixed retinal folds up to 3, 6, and 9 clock hours of the fundus respectively. Grade D (massive) has retinal folds in all four quadrants and giant star folds of the entire retina, which forms a funnel-like configuration about the optic nerve head. Grade D-1 denotes a wide, open funnel; D-2, a narrow funnel with an anterior entrance of 45° or less; and grade D-3, a closed funnel, when the optic disc is obscured from view.

We have retrospectively reviewed the records of 75 consecutive cases of total retinal detachment associated with the more advanced grades of PVR and treated with scleral buckling, closed vitrectomy, and intravitreous air-fluid exchange, operated on by one of us (JWM) between 1976 and 1980. These cases were classified according to the newly proposed PVR system. Their clinical features and the treatment results are presented herein.

Materials and methods

All patients had a complete ophthalmic examination preoperatively. The anterior segment findings, including gonioscopy and dynamic vitreous biomicroscopy with a three-mirror contact lens,[17] were recorded by detailed diagrams. Two observers examined the fundus with a small-pupil ophthalmoscope[18] and scleral indentation, and the findings were recorded in large, colour-coded fundus drawings. Cases of penetrating ocular injury or diabetic retinopathy were excluded from this study.

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All eyes were operated on under general anaesthesia. We performed 360° scleral buckling with an intrascleral silicone implant and an encircling band, with diathermy treatment to the lamellar scleral bed. Posterior retinal breaks were closed by radial implant under the circumferential buckle. Closed vitrectomy was performed to excise the central core of vitreous gel, the transvitreous membranes, and most of the intravitreous and preretinal membranes that could be removed easily. No vigorous attempts were made to dissect retinal star folds or to peel epiretinal membranes. Subretinal fluid was released in the scleral bed with concomitant intravitreous air injection. We performed lensectomy only when vitrectomy could not otherwise be undertaken safely because of lens opacities obstructing the fundus from view. Postoperatively the patient was placed in a prone position until the intravitreous air bubble resorbed. All successful cases of retinal reattachment were followed up for at least six months.

Results

The study included 75 eyes (45% right eye, 55% left eye) of 75 patients (61% male, 39% female). The ages ranged from 13 to 87 years, mean 54 years. All eyes had total retinal detachment with fixed retinal folds associated with the more advanced grades of PVR, 25 eyes with marked PVR (grade C), and 50 eyes with massive PVR (grade D).

57% of our patients had had at least one previous unsuccessful operation to reattach the retina (Table 1); 24% had had more than one retinal procedure. Retinal detachment of more than 3 months' duration was recorded in 29% of the eyes. History of blunt ocular trauma was obtained in 11% of the cases and of uveitis in 7%.

Aphakia was found in 64% of our cases, including 4% of eyes with intraocular lenses. In 45% of cases retinal breaks could not be detected. Preoperative visual acuities were all worse than 6/120 but were at least light perception.

The retina was reattached with one operation in 36 of the 75 eyes (48%) (Table 2). Of the 39 eyes in which the retina either remained detached or became redetached after the initially successful operation 12 underwent a second operation. In the remaining 27 cases either the detachment was deemed inoperable because of poor visual prognosis and increased surgical risks, or the patient declined further surgery. In four of the 12 cases that had a second operation the retina was attached. A third operation was further undertaken in two of the eight eyes in which the second operation was unsuccessful, and in both cases the retina was reattached, yielding an overall cumulative success rate of 56%. There was a tendency for the reattachment rate to decrease with advancing severity of PVR.

Table 2 *Cumulative success rate*

Grade of PVR	*No of eyes*	*One operation (all eyes)*	*Two operations (12 eyes)*	*Three operations (2 eyes)*
C-1	5	100%	—	—
C-2	5	100%	—	—
C-3	15	60%	60%	73%
D-1	13	46%	54%	—
D-2	18	39%	50%	—
D-3	19	21%	26%	—
Total	75	48%	53%	56%

Table 3 shows the postoperative visual acuity in the 42 eyes with retinal reattachment. Postoperative visual acuity of 6/30 or better was achieved only in eyes with the less severe grades of PVR (grades C-1 to C-3). In 22 eyes despite retinal reattachment visual acuity was worse than 6/120. All eyes had at least light perception. Causes of poor postoperative vision included retinal folds extending to the macula in eight eyes, macular pucker in six eyes, keratopathy in three eyes, pigmentary maculopathy in two eyes, chronic cystoid maculopathy in two eyes, and central retinal vein obstruction in one eye.

Table 1 *Initial findings*

Grade of PVR	*No. of cases*	*Cases with prior retinal operation*	*Retinal detachment >3 months duration*	*Aphakia*	*Retinal breaks*		
					None observed	*One break*	*More than one break*
C-1	5	2 (40%)	0	0	1 (20%)	4 (80%)	0
C-2	5	4 (80%)	1 (20%)	3 (60%)	3 (60%)	2 (40%)	0
C-3	15	8 (53%)	4 (27%)	10 (67%)	9 (60%)	3 (20%)	3 (20%)
D-1	13	8 (62%)	3 (23%)	9 (69%)	8 (62%)	1 (8%)	4 (30%)
D-2	18	9 (50%)	2 (11%)	12 (67%)	7 (39%)	6 (33%)	5 (28%)
D-3	19	12 (63%)	12 (63%)	14 (74%)	6 (32%)	6 (32%)	7 (36%)
Total	75	43 (57%)	22 (29%)	48 (64%)	34 (45%)	22 (30%)	19 (25%)

Table 3 *Postoperative visual acuity in anatomically successful cases**

Grade of PVR	*No of eyes with retinal reattachment*	*6/6 to 6/12*	*6/15 to 6/30*	*6/60 to 6/120*	*CF*	*HM*	*LP*
C-1	5	1	3	0	0	1	0
C-2	5	0	2	1	2	0	0
C-3	11	0	1	7	2	1	0
D-1	7	0	0	1	5	1	0
D-2	9	0	0	2	4	3	0
D-3	5	0	0	2	1	1	1
Total	42	1	6	13	14	7	1

*CF indicates counting fingers, HM hand movements, LP light perception

Table 4 *Intraoperative complications*

Complication	*No of eyes*	*Failure*	*Success*
Scleral perforation	6	3	3
Intraoperative choroidal haemorrhage	3	3	0
Iatrogenic retinal break	2	2	0
Lens damage	1	1	0
Retinal incarceration	1	0	1
Total	13	9	4

The 14 reoperations in 12 eyes (16%) included revision of scleral buckle, repeat vitrectomy, lensectomy, air-fluid exchange, and choroidal tap. Lensectomy was performed in seven eyes either as part of the initial operation or during reoperation.

The retina was not reattached in 33 eyes (44%). Severe PVR with fibrous membrane densely adherent to the retina accounted for most of these cases (24 cases, 32%), and intraoperative complications contributed to the failure rate in nine cases (12%). However, in four other eyes in which intraoperative complications also occurred the retina was reattached (Table 4). Eleven of the 13 eyes complicated by intraoperative mishaps had had one or more previous scleral buckling procedures before they were treated by us.

Discussion

The results of any study involving the surgical management of retinal detachment depend on the number of cases with PVR included in the study and the severity of the PVR. An excellent success rate could be obtained when only the least severe cases of PVR were included, and conversely poor treatment results could occur when most of the cases had the most advanced grades of PVR. A uniform classification system of PVR provides a means of substratifying this condition by degree of severity so that comparison of the different treatment methods is meaningful. Since this classification has been introduced only recently, there are no established reports with which the present series could be compared.

We have shown that scleral buckling with closed vitrectomy and intravitreous air injection can reattach the retina and salvage vision in many eyes with marked or massive PVR. However, the retinal detachment in 44% of our cases was not successfully repaired. The contributing causes of failure in these 33 eyes were retinal redetachment from severe PVR (32%) and intraoperative complications (12%). The surgical procedures of scleral buckling, vitrectomy, and intravitreous air injection treated only the clinical results of the PVR process but did not affect the pathogenetic mechanism that produced the condition. Thus, even when the operation was successful initially in reattaching the retina before the PVR process had run its course, further membrane contraction could cause redetachment. Since membrane proliferation and contraction follow a variable and unpredictable course, it is impossible to determine the optimal time for reattachment surgery.[10] Thus, in addition to mechanically repairing the retinal detachment by physically neutralising the forces opposing retinal reattachment, it is also advisable to pay attention to the basic problem of cellular proliferation from which PVR arises. Cellular proliferation has been inhibited with intravitreous injection of antimetabolites in experimental animal models.[11-13] Early success and no serious toxicity have also been reported in human studies using 5-fluorouracil.[13] The pharmacological management of PVR, either alone or with other types of treatment, would best be determined by future well-designed randomised studies.

Many of our PVR cases were lost not only owing to continuous proliferation of cellular membranes, but also to posterior and peripheral retinal breaks that were held open by persistent traction. A large air bubble injected into the vitreous cavity both acts as a volume expander after release of subretinal fluid to flatten the retinal folds, and also provides tamponade to retinal breaks. However, when the air is resorbed in the course of a few days, and before chorioretinal adhesion is established, residual and persistent vitreoretinal traction ultimately results in redetachment. Thus permanent intraocular tamponade by the use of substances such as hyaluronic acid and silicone oil seems desirable.[20] Silicone oil has been reported to provide a promising approach to repair complicated retinal detachments.[9,20,21] The potential for using these and other viscoelastic substances in the management of PVR remains to be explored and confirmed.

Intraoperative complications occurred in 17% (13 eyes) in our series. Many of these eyes had undergone multiple ocular operations previously. Extensive extraocular and intraocular procedures in these very poor eyes frequently led to failure. The sclera adjacent to the scleral buckle could have been damaged by prior cryotherapy, diathermy, scleral suturing, or dissection, and further manipulation of the friable and diaphanous tissue is often complicated by scleral perforations. Moreover, the operative risks inherent in closed vitrectomy are substantially increased when the detached retina is drawn anteriorly by centripetal traction exerted by a contracting equatorial transvitreous membrane, thus diminishing the anterior vitreous space into which the vitrectomy instruments must be introduced. Perhaps in the presence of severe PVR vitrectomy with an open-sky approach,[22] which offers more freedom of movement with the instruments, better visualisation, and more precise handling of the preretinal membrane, might yield an improved prognosis. In another study we had shown that in the previtrectomy era many eyes with retinal detachment and severe PVR could be successfully repaired with scleral buckling alone.[23] Perhaps scleral buckling alone should be considered as the primary surgical procedure in selected cases in which closed vitrectomy carries significant risks

Retinal detachment complicated by severe PVR requires a multidimensional approach, including adequate chorioretinal adhesion, conventional scleral buckling procedure, microsurgical intraocular manoeuvres, long-term internal tamponade, and inhibition of cellular membrane proliferation. In the light of the increased morbidity and complication rates from extensive operative procedures in these eyes, and the unknown long-term toxic effect of some of the pharmacological agents and viscoelastic vitreous substitutes, it is prudent to consider the risk-benefit ratio when selecting the optimal surgical procedure for each case of PVR. Perhaps in less severe cases scleral buckling alone might suffice to effect retinal reattachment.[23] In more advanced cases vitrectomy combined with scleral buckling and internal tamponade might offer a better result. And in the most severe cases a combination of all available methods might seem necessary. The controversy about which combination of surgical procedures is most effective and appropriate for PVR cases of various degrees of severity suggests that retinal surgeons, while adopting their individually preferred approach, should present their results in such a way that meaningful statistical comparisons can be made.

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Hyperprolinaemia and gyrate atrophy of the choroid and retina in members of the same family

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SUMMARY A report is given of the occurrence of asymptomatic hyperprolinaemia type I in the father of a family in which two of the children have gyrate atrophy of the choroid and retina.

Gyrate atrophy of the choroid and retina is an autosomal recessive disease[1] due to deficient activity of the enzyme ornithine ketoacid aminotransferase. There is resultant hyperornithinaemia, hyperornithinuria,[2,3] and hypolysinaemia.[4]

The typical eye findings are of circular areas of total choroidal and retinal atrophy, beginning at the periphery. There is hyperpigmentation in the more intact retina around the areas of atrophy. It is associated with myopia, and there may be vitreous opacities. The electroretinogram (ERG) may be initially normal[1] but with time usually becomes severely depressed or unrecordable. There are abnormalities of electro-oculogram (EOG) and dark adaptation. Defects of the retinal pigment epithelium and choriocapillaris appear on fundus fluorescein angiography.

Generalised manifestations include muscle weakness, abnormal electromyogram (EMG), and atrophy of type II muscle fibres, with tubular aggregates on electron microscopy,[5] abnormal electroencephalograph (EEG) or seizures[6] and abnormal ERG.[5] Clinically these changes are usually mild or absent.

Ornithine aminotransferase is lacking in fibroblasts[7] and lymphocytes.[8] This enzyme converts ornithine into Δ-pyrroline-5-carboxylic acid (Fig. 1).

Hyperprolinaemia is an autosomal recessive disease.[9] There are two types. Type I is due to deficient proline oxidase activity, and type II is due to deficient Δ-pyrroline-5-carboxylic acid dehydrogenase activity (Fig. 1). Both types are usually asymptomatic. In type I cases disease of the renal and central nervous systems, delayed neurological development, seizures, and EEG changes have been recorded, but no direct connection has been established between these manifestations and the disease.[9] Similarly, some patients with type II hyperprolinaemia have had retarded mental development and seizures, but again no direct association has been established.[9]

BIOCHEMISTRY

The biochemical relationship between proline and ornithine metabolism is shown (Fig. 1). Proline is a non-essential amino acid. Amino acids occur in the body fluids in the free form and in peptide linkage. Proline is involved in brain metabolism, and cerebrospinal fluid (CSF) proline is increased in type I and type II hyperprolinaemia.[9] Proline is abundant in its free form, and important pathways provide for its biosynthesis and degradation.

The proline derivative Δ-pyrroline-5-carboxylic acid provides a link between the urea and tricarboxylic acid cycles.

Hydroxyproline, found in peptides and proteins, arises by post-translational modification of peptide proline. Excess proline regulates its metabolism to enhance outflow through the ornithine pathway. Proline competes with hydroxyproline and glycine for a common membrane carrier, which serves their uptake preferentially at concentrations in excess of 0·1 mM. As either amino acid (proline, hydroxyproline) proceeds to saturate its renal transport system, competitive inhibition of the transport of the other amino acid and glycine occurs. Renal parenchyma has a significant role in proline uptake and metabolism.[9]

Aminoglycinuria (proline, hydroxyproline, glycine) occurs when plasma proline is greater than 0·8 mM. The intensity of the aminoglycinuria is proportional to the degree of hyperprolinaemia. Hyperprolinuria results from the progressive saturation of the proline reabsorption sites in the renal

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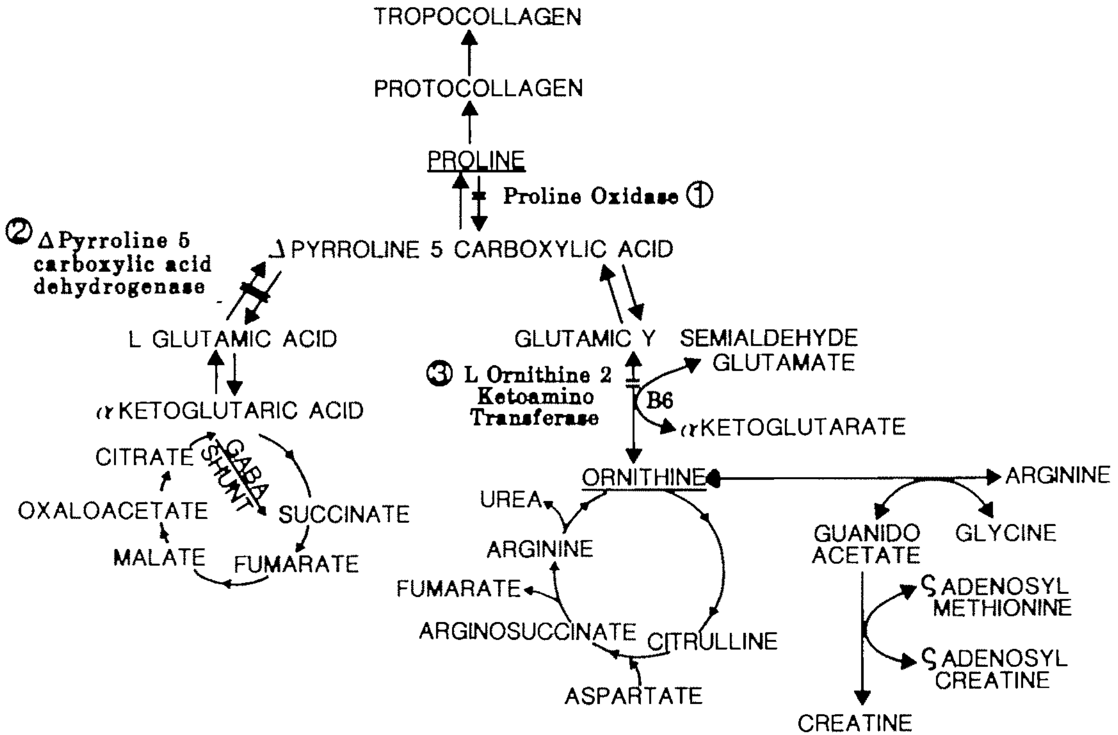

Fig 1 *Pathways of ornithine and proline metabolism*

tubule. Prolinuria thus results from an overflow mechanism. Hyperglycinuria and hyperhydroxyprolinuria is due to a competitive inhibition of the site shared by the three substrates.[9]

Proline accumulation is greater in type II than in type I hyperprolinaemia. The degradation of proline to glutamic acid through the proline intermediary is less efficient than normal in type I hyperprolinaemia. The enzyme proline oxidase involved in type I hyperprolinaemia is a mitochondrial, membrane bound enzyme.[9]

Ornithine arises from dietary or endogenous arginine by (1) action of arginase, (2) the arginine-glycine transamidase reaction—the first enzyme in the pathway of creatine synthesis. The major enzymes of ornithine metabolism are intramitochondrial, the ornithine entering the mitochondria through a specific transport system. The major pathway for the disposal of excess ornithine is through the mitochondrial enzyme ornithine ketoacid/aminotransferase, which needs pyridoxal phosphate as cofactor.[10] It is this enzyme which is deficient in gyrate atrophy with hyperornithinaemia.

Case reports

The family under examination consists of father (case 1), mother (case 2), elder son (case 3), younger son (case 4), and daughter (case 5).

The daughter was first seen in 1971 aged 9 years, having been referred because of poor visual acuity. Myopia of mild degree (−2·0 sphere right eye; −2·5 sphere left eye) was found. Three years later her myopia had increased to a −9·0 sphere with −0·5 cyl at 20° in the right eye and −9·0 sphere with −1·0 cyl at 155° in the left eye. With this correction her vision was 6/9 in both eyes. Her fundi at this time showed the typical peripheral changes of stage I of gyrate atrophy (Figs. 2a and b). Central field testing gave normal results, but typical concentric constriction of the peripheral fields was present on perimetry.

At that time her younger brother (case 4), aged 8 years, was referred with poor visual acuity. He also had myopia of −3·0 sphere in the right eye and −2·5 sphere in the left. Fundal examination showed an almost identical stage I picture to that of his sister. (Figs. 3a and b). A small retinal operculum was noted in his right eye. Central fields were again full, with peripheral field constriction.

Lens changes were absent in both children. The children were referred for electrophysiology, which was normal. An initial diagnosis of cobblestone degeneration was made.

Although the myopia in both children continued to

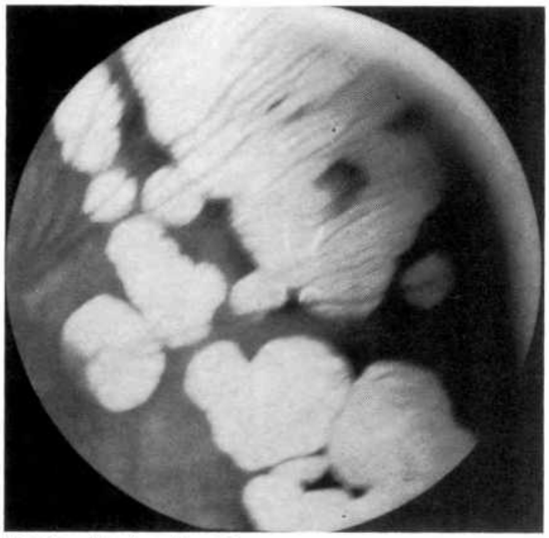

Fig. 2a *Fundus of case 5.*

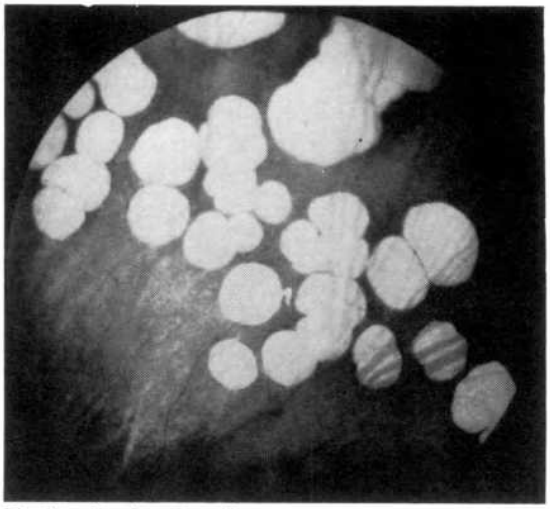

Fig. 2b *Fundus of case 5.*

increase, their visual acuity was maintained, and they had no subjective symptoms.

Several years later it was decided to assess their plasma and urinary ornithine levels. A fasting amino acid profile of blood and urine was therefore undertaken. The results are shown in Tables 1 and 2. There was a hyperornithinuria, hyperornithinaemia, and hypolysinaemia, confirming the diagnosis of gyrate atrophy of the choroid and retina, although electrophysiological testing at that time was still normal.

Both children were treated with pyridoxine, which has a lowering effect on plasma ornithine,[11] and a low protein diet which amino acid supplements. However, this was abandoned because of poor compliance and because of the apparent slow nature of the disease. Fasting amino acid profiles were also undertaken of the father, mother, and elder brother of the affected children (Tables 1, 2).

The elder son (case 3) showed an elevated plasma proline and a high normal ornithine level, though urinary levels of these were normal. At the late age of 22 years, this son developed myopia, having previously had normal visual acuity and a normal refraction. The most interesting results were those of the father. The blood sample showed a high normal ornithine as might be expected from the parents,[1]

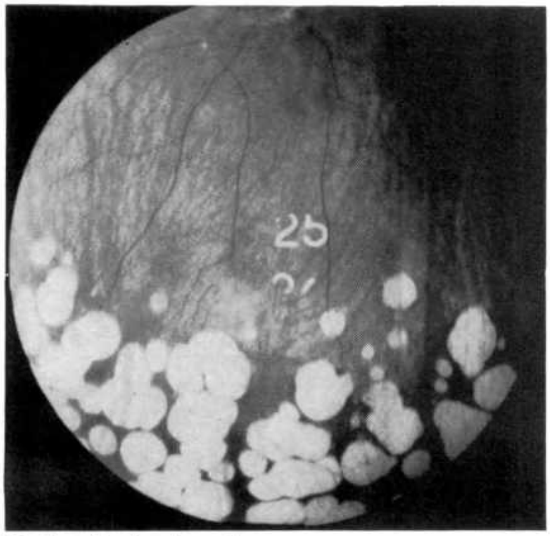

Fig. 3a *Fundus of case 4.*

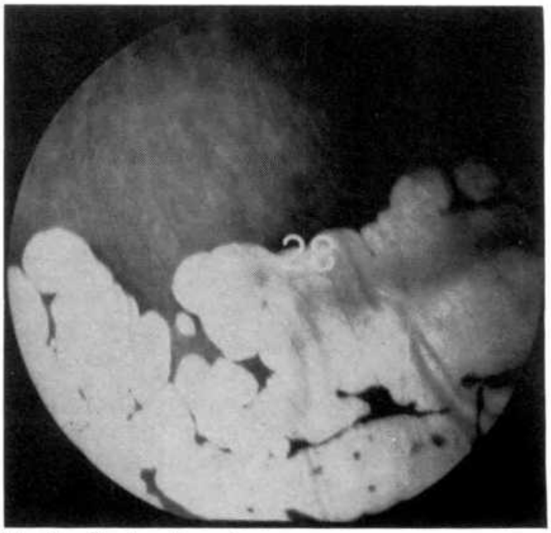

Fig. 3b *Fundus of case 4.*

Table 1 *Biochemical amino acid profile: plasma*

Plasma amino acids in mmol/l	*Case 1 (father)*				*Case 2 (mother)*		*Case 3 (elder son)*		*Case 5**		*Case 4**	
	Results 1		*Results 2*									
Hydroxyproline	ND	–	21	N	ND	–	41·8	HN	26·6	N	25·2	N
Glutamic acid	104	N	48·7	N	33	LN	75·8	N	111	N	82·6	N
Proline	1079	+++	931	+++	281	HN	554	+	285	HN	353	HN
Glycine	244	N	265	N	214	N	307	N	228	N	195	N
Ornithine	142	HN	92 5	N	89 6	N	139	HN	818	++++	659	++++
Lysine	193	N	202	N	148	N	135	N	81 7	–	99	LN
Arginine	58·4	N	93·4	N	73 1	N	42 8	LN	76	N	83 1	N

*Patients affected with gyrate atrophy
+=increased. –=decreased HN=high normal LN=low normal. N=normal ND=none detected.

who are often obligate heterozygotes.[1 12] However, it also showed a markedly elevated plasma proline level. Proline and ornithine levels were normal in his urine (Tables 1, 2).

Further fasting blood and urine samples were taken from the father. (Results 2 in Tables 1, 2) to establish the type of hyperprolinaemia. The plasma again showed a high proline level, though the urine showed only a high normal level. There was no increase in the excretion of Δ-pyrroline-5-carboxylic acid as would occur in type II hyperprolinaemia. It was therefore concluded that this was a type I hyperprolineamia. Further provocative testing with ornithine loading in both parents[1] was unfortunately impossible for economic and social reasons.

The visual progress of the two affected children, the girl now aged 20 years, and the younger son aged 16 years, remains surprisingly good. Their fundal appearances are still those of stage I. They are considerably hindered by night blindness, and their perimetry shows considerable constriction, although their central fields remain full. Normal visual acuity is maintained with their myopic correction. Dark adaptation tests are only moderately abnormal. Recent ERG and EOG examinations have not been possible because of poor compliance.

BIOCHEMICAL METHODOLOGY

The biochemical tests were performed on fasting subjects, and consisted of a blood sample and 24-hour collection of urine.

Deproteinisation of plasma prior to aminoacid analysis was employed by using 50 mg of salicylsulphonic acid per ml plasma. Urine specimens were treated similarly to adjust the pH prior to application to the resin column. A Technicon TSM amino acid analyser was employed with separation of the individual plasma amino acids requiring approximately 6½ hours. A Wang 2200 computer was used to process and evaluate the results obtained from the analyser. The findings were assessed against age-related reference ranges with the symbols N, HN, + or – being appended. Those results with + or –1 standard deviation (SD) of expected mean values were shown as N, those between +1 SD and +2 SDs as HN, and those between +2 SDs and +3 SDs as + etc.

The reference ranges for fasting plasma proline, hydroxyproline, and ornithine concentrations in subjects aged 8 or 9 and in adults are shown in Table 3.

Discussion

For social, psychological, and economic reasons it was not possible to carry out full investigations in this family, including enzyme studies and loading tests. However, the genotype of some family members with respect to hyperprolinaemia on the one hand and

Table 2 *Biochemical amino acid profile: urine*

Urine amino acids in mmol/l	*Case 1 (father)*				*Case 2 (mother)*		*Case 3 (elder son)*		*Case 5**		*Case 4**	
	Results 1		*Results 2*									
Hydroxyproline	ND	–	2·7	LN	ND	–	ND	–	ND	–	ND	–
Proline	6·6	N	8·5	HN	2·1	LN	2·8	N	3·9	N	6	N
Glycine	190	N	259	N	122	N	177	N	299	HN	230	N
Ornithine	23	N	ND	LN	1·7	N	1 9	N	105	++++	175	++++
Lysine	27·2	N	26·5	N	16·8	N	16·8	N	53·2	HN	76·8	HN

*Patients affected with gyrate atrophy
+=increased –=decreased HN=high normal. LN=low normal N=normal ND=none detected

Table 3 *Plasma amino acids (μmol/l)*

	Age	*Geometric mean*	*±1 SD*	*±2 SD*	*±3 SD*
Proline	3–12 yr	192·7	118·3–313·9	72·6–511·2	44 6–832·6
	>12 yr	192·4	134 8–274·8	94·4–392·3	66·1–560
Hydroxyproline	3-12 yr	30 2	17·7–51·5	10·4–87·9	6·1–150
	>12 yr	23·4	16 3–33·4	11·4–47·7	8·0–68·2
Ornithine	3-12 yr	67·3	36 4–124·5	19·7–230·2	10 6–425·8
	>12 yr	85·9	58 1–126·8	39·4–187 4	26·6–276·8

gyrate atrophy on the other may be inferred from the available data.

On the basis of the above results the father would appear to be suffering from type I hyperprolinaemia. It is somewhat surprising that he shows no aminoaciduria; indeed his hydroxyproline levels are undetectable and are therefore reduced from normal levels, as indeed they are in all three of his children. This may be explained by a relatively high renal threshold for proline.

As the father appears to have hyperprolinaemia type I, it would be expected that each of his offspring would be heterozygous for this condition, and it is of interest that his elder son (case 3) showed a raised plasma proline level and his other son and daughter (cases 4 and 5) showed high normal levels. However, it may also be noted that his wife also showed a high normal proline level. Moreover in two patients affected with gyrate atrophy in two families studied by Yatziv *et al*[12] levels of 210 μmol/l and 185 μmol/l were recorded. These correlate with the reading for the daughter.

The plasma proline levels in patients with gyrate atrophy tend to be normal and their tissue levels tend to be low.[9, 11] The elder brother and sister (cases 3 and 5) appear to have gyrate atrophy with hyperornithaemia, based on the high plasma levels or ornithine, increasing myopia, night blindness, and fundus appearances, typical of gyrate atrophy. The parents must be assumed to be obligate heterozygotes, and, although the high normal plasma ornithine in their elder son (case 3) might suggest that he is also a heterozygote, it is not possible to conclude this without further tests.

This family is of interest in that the members of consecutive generations have two genetically distinct rare recessive disorders which involve enzyme deficiencies affecting related metabolic pathways. The enzymes concerned are both mitochondrial—proline oxidase residing in the inner mitochondrial membrane, and ornithine ketoacid aminotransferase residing in the mitochondrial matrix. Although it is possible that some members of the family were heterozygous for each condition, or homozygous for one and heterozygous for the other, there is nothing in the present study to suggest an interaction between the two metabolic disorders.

I am extremely grateful to Dr Robert W Logan, consultant medical biochemist, and his staff at Yorkhill Children's and Maternity Hospital, Glasgow, for their invaluable help and assistance regarding the complex biochemistry involved in this paper and also for the biochemical methodology

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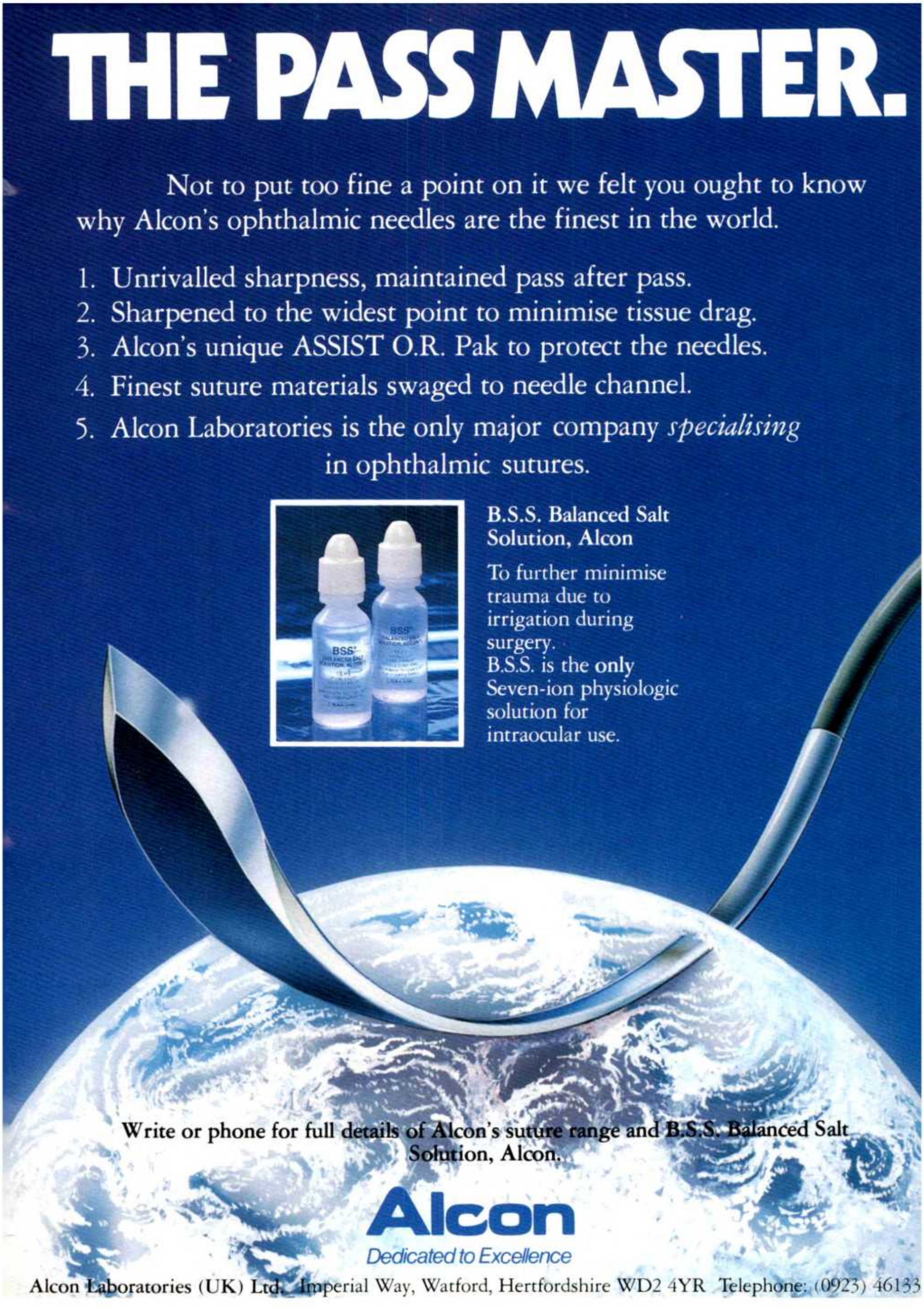

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Long-term ocular hypotensive effect of levobunolol: results of a one-year study

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SUMMARY Data for the first 12 months are reported for an ongoing, multicentre, clinical study comparing the long-term, ocular hypotensive efficacy and safety of topical levobunolol (0·5% and 1%) and timolol (0·5%). This study was a double-masked trial testing 88 patients with chronic open angle glaucoma or ocular hypertension. During the 12-month period drops were instilled twice daily into both eyes after a washout of prestudy ocular hypotensive medication. The effect of the three treatments in reducing intraocular pressure (IOP) was similar. Mean IOP reductions over the 12 months averaged 7·2 mmHg for the 0·5% levobunolol group, 6·2 mmHg for the 1% levobunolol group, and 6·0 mmHg for the timolol group. Decreases in mean heart rate of up to 5 beats per minute were observed in the 0·5% levobunolol group, up to 8 beats per minute in the 1% levobunolol group, and up to 4 beats per minute in the timolol group. Several patients were removed from the study owing to side effects possibly related to levobunolol treatment.

Several short-term studies conducted to investigate the ocular hypotensive effect of various concentrations of topical levobunolol, a non-cardioselective beta-adrenergic blocking agent, have indicated that a maximal pressure reducing effect occurs with the 0·5% and 1% concentrations.[1 2] Further comparison testing with the levobunolol vehicle over a three-month time period has confirmed the sustained ocular hypotensive effect produced by these two concentrations of levobunolol over a longer time period.[3]

Because of the progressive nature of glaucoma and the possibility of long-term drift occurring with continued use of topical beta-adrenergic blocking agents[4 5] it is particularly important to assess long-term drug effect when evaluating these drugs. Therefore the present study, a parallel, double-masked clinical trial, was designed to test the efficacy and safety of 0·5% and 1% levobunolol compared with 0·5% timolol in patients with chronic open-angle glaucoma (COAG) or ocular hypertension (OHT) for a period of one year. As most of the patients participating in the study had successfully controlled intraocular pressure (IOP) while receiving study treatments, the study was extended for a second year and is still continuing. We report here the results of the first year of treatment.

Patients and methods

Before being entered in the trial the patients were examined to determine their suitability for it. All patients participating in the study were required to have COAG or OHT with an untreated intraocular pressure of 23 mmHg or higher in each eye and none of the following conditions: (1) known contraindications to systemic or topical use of ß-blocking agents; (2) use of adrenergic-augmenting psychotropic drugs; (3) use of topical or systemic corticosteroids; (4) severe diabetes requiring changes in insulin dosage; (5) pregnancy, expected pregnancy, or lactation; (6) aphakia, chronic ocular inflammation, or any corneal abnormalities preventing reliable applanation tonometry; (7) severe COAG uncontrolled by concomitant administration of two or more antiglaucoma drugs; (8) inability to tolerate washout of prestudy antiglaucoma medications; (9) contact lens wear during the study.

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Table 1 *Examination variables and study schedule*

Study period	*Patient history*	*IOP*	*Visual field*	*Visual acuity*	*Pupil size*	*Corneal sensitivity*	*Schirmer test*
Prestudy	X	X	X	X			
Day 1 (baseline)		X		X	X	X	X
Day 4		X		X	X	X	
Week 1		X		X	X	X	
Week 2		X		X	X	X	
Week 3		X		X	X	X	
Week 4		X		X	X	X	X
Week 6		X		X	X	X	
Week 8		X		X	X	X	
Week 10		X		X	X	X	
Week 12		X		X	X	X	X
Week 16		X		X	X	X	
Week 20		X		X	X	X	
Week 24		X	X	X	X	X	X
Week 32		X		X	X	X	
Week 40		X		X	X	X	
Week 48		X	X	X	X	X	X

CBC=complete blood count.

After fulfilling these conditions the participating patients signed consent forms and underwent a washout period of prestudy antiglaucoma medication. This washout period lasted two days for pilocarpine, three days for carbonic anhydrase inhibitors, and two weeks for epinephrine, dipivefrin, or timolol. After washout the patients were randomly assigned to one of the three treatment groups (0·5% levobunolol, 1% levobunolol, or 0·5% timolol) and were instructed to instill a single drop of medication, whose nature was unknown to the physician or patient, into each eye at 9 am and 9 pm daily for the 12-month study period.

Study variables listed in Table 1 were evaluated at baseline and at 15 return visits during the one-year study period. At return visits the IOP was measured prior to instillation of the morning medication. Applanation tonometry was used to measure IOP and the Schirmer tear test on anaesthetised eyes to measure tear production. Corneal sensitivity was measured by touching a wisp of cotton to the centre of the cornea and grading the blink response.

Table 2 *Demographic data and diagnosis (number of patients in parentheses)*

Variable	*0·5% Levobunolol* (n=31)	*1% Levobunolol* (n=31)	*0 5% Timolol* (n=26)
Age			
Mean	59·5	59·9	64·0
SD	10·7	10·1	10·3
Range	42–76	31–80	45–87
Sex			
Male	11	12	10
Female	20	19	16
Race			
Caucasian	31	31	26
Non-Caucasian	0	0	0
Iris colour			
Blue	3	14	9
Green	11	6	9
Brown	17	10	8
Black	0	1	0
Diagnosis			
OHT	20	24	17
COAG	11	7	9

Biomicro-scopic eye exam.	*Ophthalmo-scopic eye exam.*	*Heart rate*	*Blood pressure, systolic/diastolic*	*Auscultation of heart and lungs*	*ECG*	*CBC/blood chemistry*
X	X	X	X	X	X	X
X	X	X	X			
X	X	X	X			
X	X	X	X			
X	X	X	X			
X	X	X	X			
X	X	X	X	X		X
X	X	X	X			
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X	X	X	X			
X	X	X	X	X	X	X
X	X	X	X			
X	X	X	X			
X	X	X	X	X	X	X

Patients could be removed from the study for administrative reasons not associated with the treatment, or their treatment could be terminated owing to adverse reactions to the test treatments or because of inadequately controlled IOP. In patients receiving prestudy antiglaucoma drugs an uncontrolled IOP was defined as an IOP that was significantly greater (>5 mmHg) than prewashout values at two consecutive visits. In patients receiving no prestudy antiglaucoma drugs an uncontrolled IOP was defined as an IOP that was not decreased by at least 20% of the pretreatment value at two consecutive visits.

A two-way analysis of variance (ANOVA)[6] was used to compare mean values at baseline and mean change from baseline at each return visit among the treatment groups for the following variables: age, IOP, pupil size, Schirmer tear test results, heart rate, and systolic and diastolic blood pressure. Right and left eye values were averaged for analysis of IOP, pupil size, and Schirmer tear test results. An ANOVA model for repeated measures[7] was used to compare treatment effects for these variables (except age) over the entire study period. Race, sex, iris colour, and prestudy medical and ophthalmololgical histories were analysed by the generalised Cochran-Mantel-Haenzel procedure.[8] All other variables evaluated were analysed by descriptive statistical methods, namely, counts, means, frequencies. For all analyses a p value ≤0·05 was considered statistically significant.

Results

DEMOGRAPHICS AND PATIENTS' HISTORIES

Of the 88 patients participating in the study 31 were in each of the levobunolol groups and 26 were in the timolol group. The distribution of patients with regard to age, sex, race, iris colour, and disease diagnosis is presented in Table 2. No significant differences were observed among the treatment groups in any demographic or medical history variables evaluated except cardiovascular disorders. The timolol group had a significantly greater proportion of patients with diagnosed cardiovascular disorders than either levobunolol group. No statistically significant differences were observed among the treatment groups at baseline for any of the efficacy or safety variables analysed.

PATIENT STATUS

The number of patients whose IOP was controlled during the study is shown in Table 3. Twenty-three patients in the 0·5% levobunolol group, 22 patients in the 1% levobunolol group, and 24 patients in the timolol group are continuing in the study. Five patients in the 0·5% levobunolol group, six patients in the 1% levobunolol group, and two patients in the timolol group were removed from the study because of inadequately controlled IOP, and five patients were removed for side effects thought by the investigator to be related to levobunolol treatment. Two patients, one treated with 0·5% levobunolol and one with 1% levobunolol, showed signs of ocular irritation (blepharitis, conjunctival erythema). In most cases of ocular irritation it was possible to challenge the patient with both the vehicle and a repeat exposure to the drug. In these cases ocular irritation recurred only with exposure to the drug. One patient treated with 1% levobunolol reported a subjective decrease in visual acuity which could not be con-

Table 3 *Status of patients at the end of the 12-month study period (number of patients in parentheses)*

Status	*0·5% Levobunolol* (n=31)	*1% Levobunolol* (n=31)	*0·5% Timolol* (n=26)
Ongoing/adequately controlled IOP	23	22	24
Discontinued from study*	0	1	0
Removed from study			
lack of IOP control	5	6	2
side effects	3	2	0

* For reasons unrelated to the test treatments

firmed by the investigator. One patient treated with 0·5% levobunolol complained of headaches, and another patient also treated with 0·5% levobunolol complained of heartburn and diarrhoea.

EFFICACY

The ocular hypotensive effect of the three treatments was similar: after an immediate drop in IOP at the first return visit, IOP reductions were sustained throughout the one-year trial (Fig. 1). Mean reductions in IOP from baseline ranged from 5·9 to 8·1 mmHg in the 0·5% levobunolol group, from 5·2 to 7·1 mmHg in the 1% levobunolol group, and from 4·7 to 6·9 mmHg in the timolol group. Significant differences among the groups in the magnitude of IOP reductions were seen only on the return visit at week 24, when the 0·5% levobunolol group had a significantly greater reduction in IOP than the timolol group (Table 4).

SAFETY

The graphical representation of mean heart rate over the one-year study period showed similar decreases with each of the treatments (Fig. 2). Mean decreases of up to 5 bpm were observed within the 0·5% levobunolol group, up to 8 bpm within the 1% levobunolol group, and up to 4 bpm within the timolol group. Although some individuals in each of the treatment groups had clinically significant decreases in heart rate at some of the return visits, none had a heart rate less than 55 beats per minute or a diagnosis of sinus bradycardia on electrocardiographic (ECG) examination.

Both levobunolol and timolol appeared to have little effect on systolic and diastolic blood pressure (Fig. 3). In the three treatment groups overall decreases in mean systolic blood pressure ranged from 3 to 4 mmHg and overall decreases in diastolic blood pressure from 1 to 5 mmHg.

Table 4 *Mean intraocular pressure changes from baseline (mmHg)*

Study period	*0·5% Levobunolol*		*1% Levobunolol*		*0·5% Timolol*		*Among-group p values*
	n	*Mean SD*	*n*	*Mean SD*	*n*	*Mean SD*	
Day 1 (baseline)	31	27·9 ±5·5	31	27·0±3·7	26	26·4±2·8	NS
Day 4	28	−8·1* ±4·4	31	−6·9±3·6	26	−6·9±2·9	NS
Week 1	27	7·7 ±3·3	27	−6·5±2·8	26	−5·7±3·8	NS
Week 2	28	−7·4 ±3·4	29	−6·7±3·4	24	−6·0±2·6	NS
Week 3	26	−7·0 ±3·4	28	−7·1±3·4	24	−6·3±3·2	NS
Week 4	26	−7·3 ±3·5	25	−6·5±3·0	25	−6·7±3·1	NS
Week 6	23	−7·2 ±3·0	23	−6·2±1·9	24	−6·7±3·0	NS
Week 8	23	−6·9 ±3·6	24	−6·3±2·3	25	−6·3±2·9	NS
Week 10	23	−6·9 ±3·8	21	−6·3±2·1	24	−6·5±3·1	NS
Week 12	21	−6·9 ±3·4	21	−6·4±1·7	25	−6·4±3·0	NS
Week 16	21	7·5 ±2·7	24	−6·9±2·9	24	−6·5±2·6	NS
Week 20	21	−6·8 ±2·5	23	−5·9±2·0	22	−6·1±1·9	NS
Week 24	20	−7·3 ±2·4	20	−6·2±2·5	22	−5·6±2·1	0·027†
Week 32	19	−6·5 ±2·5	19	−5·3±2·5	20	−5·4±2·3	NS
Week 40	17	−5·9 ±2·3	18	−5·4±1·9	17	−5·3±1·7	NS
Week 48	15	−6·0 ±2·5	17	−5·2±1·6	15	−4·7±1·7	NS
Overall mean change		−7·2		−6·2		−6·0	NS

* All treatment groups showed significant within-group decreases from baseline at each follow-up day (p≤0·001)

NS=not significant

† When among-group comparisons were made on day 169, mean decreases in the 0·5% levobunolol group were significantly greater than the timolol group

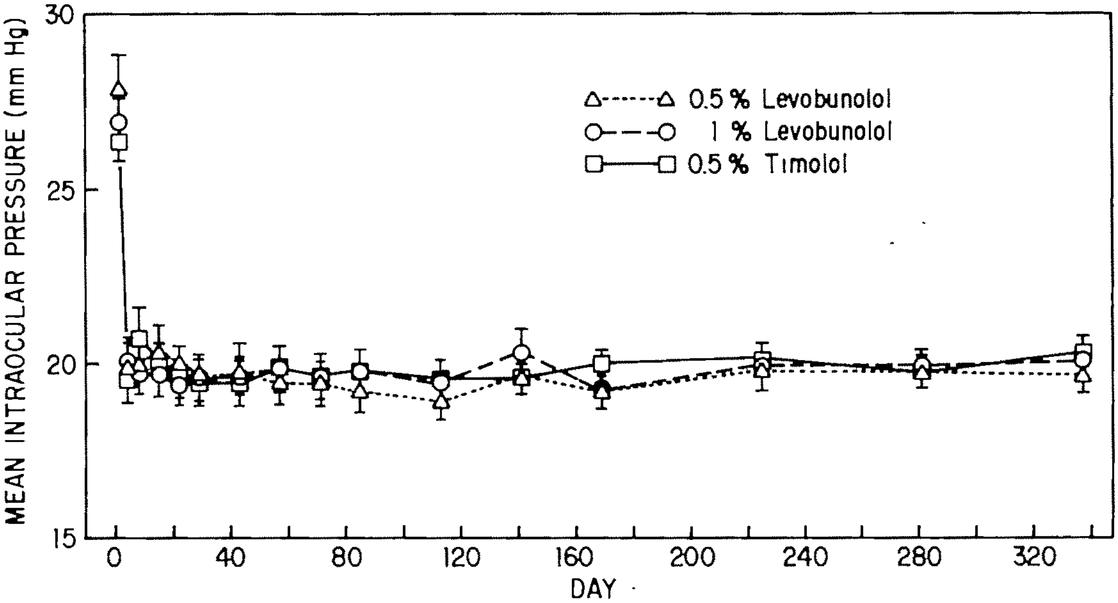

Fig. 1 *Mean IOP values after topical treatment with 0·5% levobunolol, 1% levobunolol, or 0·5% timolol.*

Few changes from baseline values were seen in visual acuity, pupil size, cup-disc ratio, corneal sensitivity, Schirmer tear test results, or biomicroscopic and ophthalmoscopic findings. Observed changes were mild and similarly distributed between levobunolol and timolol treatment groups. Only one patient treated with 1% levobunolol complained of burning and stinging, and this was at only one visit. No changes in visual fields occurred during the study. No systemic findings of note were observed during auscultation of the heart and lungs, ECG examination, or blood analysis.

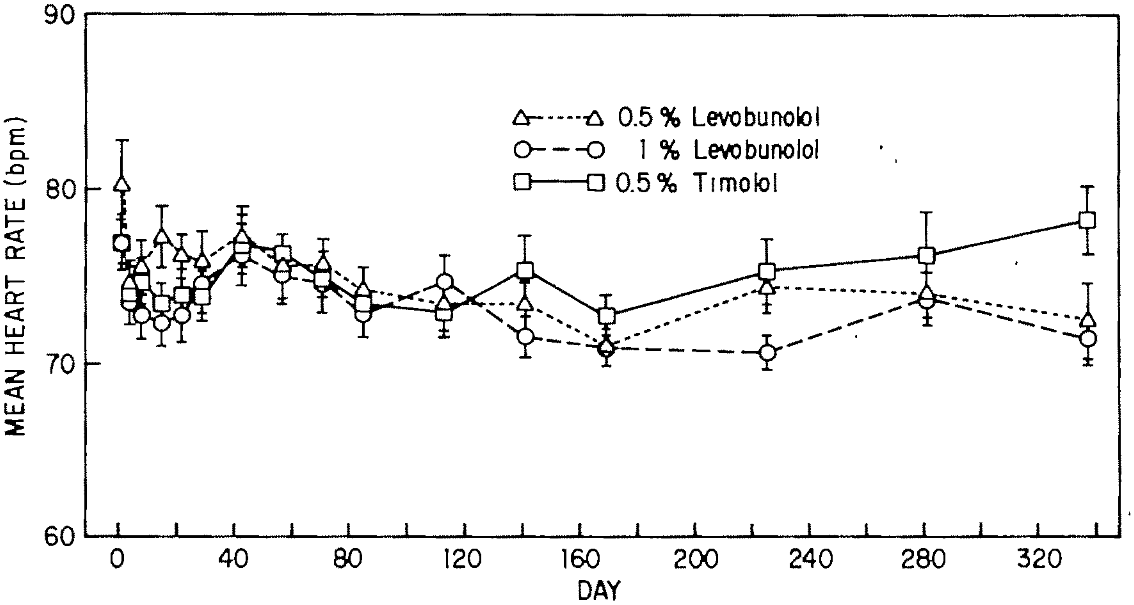

Fig 2 *Mean heart rate values after topical treatment with 0·5% levobunolol, 1% levobunolol, or 0·5% timolol.*

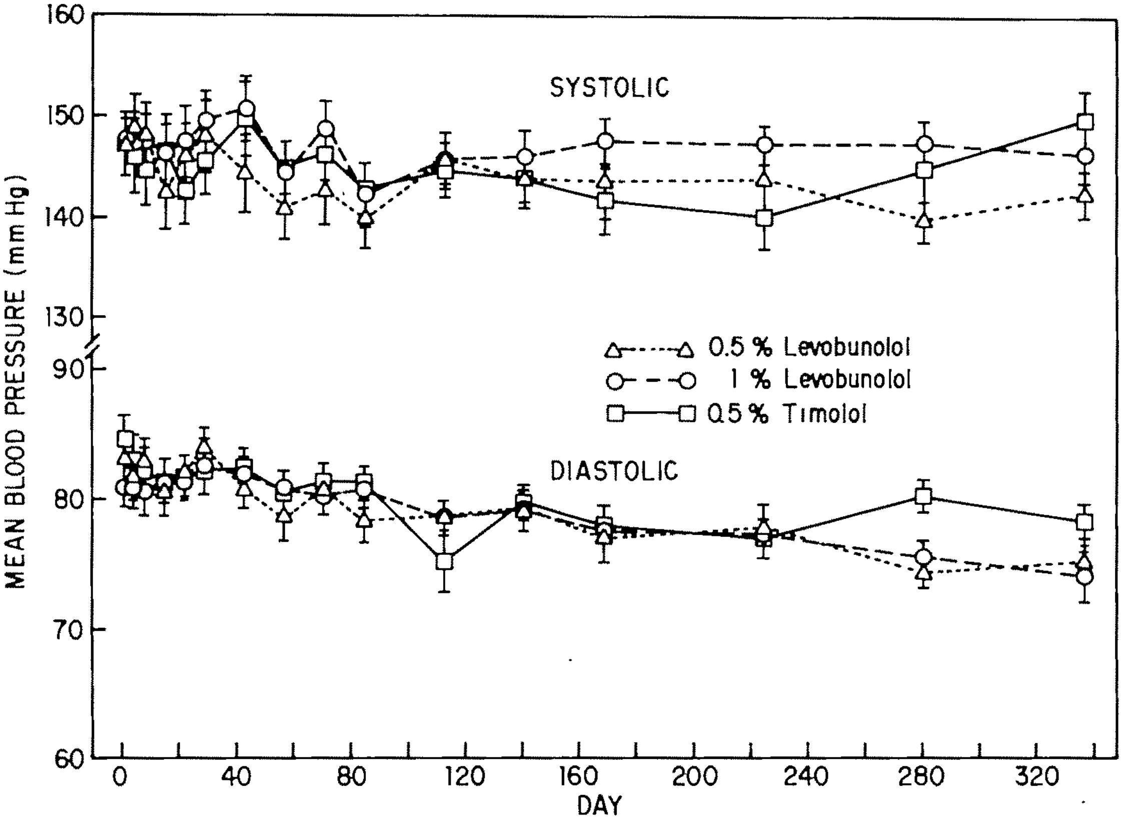

Fig. 3 *Systolic and diastolic blood pressure values after topical treatment with 0·5% levobunolol, 1% levobunolol, or 0·5% timolol.*

Discussion

The results from this year-long clinical trial confirm the long-term ocular hypotensive efficacy of levobunolol in treating elevated IOP. Topically applied levobunolol in concentrations of 0·5% and 1% produced a significant and sustained reduction in IOP in patients with chronic open-angle glaucoma or ocular hypertension. The IOP reduction produced by levobunolol was not significantly different from that produced by timolol, nor was the number of subjects removed from the study for failure of treatment significantly different among the groups.

Treatment with levobunolol was associated with few ocular side effects. No significant changes in tear production, as measured by the Schirmer test, nor in corneal sensitivity, as measured by the blink response, were noted. In this large multisite long-term study it was not feasible to use an anaesthesiometer to measure corneal sensitivity more precisely. Changes in mean heart rate and blood pressure occurring with both levobunolol treatments were not of clinical importance.

A greater number of levobunolol treated patients than timolol treated patients were removed from this study as a result of adverse experiences attributed to the test medication. However, although the signs and symptoms resulting in the removal of patients from the study were seen only in levobunolol treated patients, blepharitis,[9] conjunctival erythema,[9] headaches,[10] and diarrhoea[9] have all been reported with topical timolol usage.

In the patient complaining of 'non-specific blurring of central vision' no change in refraction was detectable.

Although long-term drift has been associated with timolol treatment,[3,4] data from this study do not suggest a significant drifting of IOP over the one-year period with either timolol or levobunolol treatment. It appears that levobunolol will be a beneficial and long-effective addition to the currently available treatments for glaucoma and ocular hypertension.

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Prolonged survival of allogeneic corneal grafts in rabbits treated with topically applied cyclosporin A: systemic absorption and local immunosuppressive effect

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SUMMARY The modes of action of topical cyclosporin A were studied in rabbits. Immunorejection of corneal allografts was provoked by placing the grafts eccentrically, in contact with the limbus. Topical application of cyclosporin A five times daily for 28 days prevented the rejection of corneal allografts. All grafts were rejected in the control animals. The seven rabbits of the cyclosporin A group were subsequently treated for six months with a lower dosage of cyclosporin A 1%. In six rabbits the graft remained clear. One rabbit treated with two drops a day showed an allograft reaction that could be suppressed by increasing the dosage. After six months, discontinuation of the therapy resulted in rejection of all grafts within four weeks. Cyclosporin A could be detected in the plasma and aqueous humour of both eyes at the end of the treatment, raising the question whether the immunosuppressive effect of topically applied cyclosporin A was due to local or systemic action. Cyclosporin A 1% was therefore applied to the fellow eye five times daily following transplantation, and this treatment, producing similar plasma levels of cyclosporin A, failed to delay the rejection of eccentric corneal allografts. Consequently the suppression of the allograft rejection by topical cyclosporin A is primarily a local immunosuppressive effect, though systemic influence is not ruled out.

Since its introduction by Borel *et al.*[1] in 1976 cyclosporin A has proved to be a powerful non-myelotoxic immunosuppressive agent and has given encouraging results in organ transplantation. Immunological rejection is the main cause of failure of corneal grafts. Administered parenterally it prolongs the survival of corneal allografts in rabbits.[2-4] However, systemic treatment with immunosuppressive agents may produce severe side effects, which are not acceptable in clinical corneal transplantation Further improvement of the results of keratoplasties will depend on the development of immunosuppressive agents that can be applied topically to reduce the risk of systemic toxicity

Hunter and coworkers[5] first reported the favourable effect of cyclosporin A 1% eye drops on the survival of corneal allografts in rabbits. They developed a new experimental model in which rejection of corneal allografts is initiated solely by the transplanted corneal antigens. By placing the allografts eccentrically in contact with the limbus, rejection is accomplished in almost 100% of the cases without additional sensitisation by a second set skin graft. This experimental model closely resembles the situation of corneal grafting in man.

Prolonged survival of corneal allografts in rabbits could be obtained by continuing topical therapy with cyclosporin A 1% eye drops for 13 weeks[6]; 44% of the corneal grafts remained clear even for longer than three months on cessation of the treatment. This observation corresponds to results achieved in other experimental organ transplants, where it is sometimes possible to achieve prolonged survival of the allograft following short-term treatment with cyclosporin A.[7 8] This paper reports experiments in which we further explore the methods of treatment with topical cyclosporin A 1% after corneal transplants in rabbits. We used the rabbit model cited above.[5 6]

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MATERIALS AND METHODS

Outbred New Zealand albino rabbits were used in this study.

EXPERIMENT 1

Corneal allografts taken from Dutch rabbits were implanted in the right eye of 15 albino rabbits. The recipient hole, 7 mm in diameter, was trephined eccentrically in contact with the limbus in the upper temporal quadrant. The donor button, 7·5 mm in diameter, was fixed with a running nylon 10-0 suture. Surgery was carried out under general anaesthesia (fluanisone 1% and fentanyl citrate 0·02%, 0·5 ml/kg intramuscularly). In addition a retrobulbar injection of 1 ml lidocaine 2% was given, and 5000 IU heparin was administered intravenously. All the keratoplasties were performed under an operating microscope by the same surgeon. At the end of surgery a single injection of 40 mg gentamicin was given subconjunctivally. The grafted eyes were divided at random into two treatment groups. Seven eyes were treated with cyclosporin A 1% in olive oil eye drops and eight eyes with sterile olive oil only. The eye drops were administered five times daily for four weeks after the operation. The evaluation was double blind.

The eyes were checked twice a week for rejection symptoms by slit lamp examination. Criteria for rejection were the occurrence of an inflammatory reaction in the anterior chamber, an endothelial or epithelial rejection line, or oedema of the graft with or without associated superficial or deep vascular penetration in a previously uninflamed eye with a clear corneal graft.

After the fourth week the code was opened and the results analysed. The seven rabbits of the cyclosporin A group were subsequently treated with a lower dose of cyclosporin A 1% drops. Four rabbits were given one drop four times a day, three rabbits were given one drop of cyclosporin A 1% twice daily. Weekly slit lamp examinations were done. After six months of topical treatment blood samples were taken from an ear vein to determine cyclosporin A plasma concentrations. Cyclosporin A levels were also determined in the aqueous humour of both eyes. The anterior chambers were punctured under general anaesthesia with a 26 gauge disposable needle through the limbus, and 0·1 to 0·2 ml of the aqueous was aspirated

Cyclosporin concentrations in blood plasma and aqueous humour were determined by radioimmunoassay[9] with a kit manufactured by Sandoz Ltd.

Blood samples drawn on heparin were kept at room temperature for two hours prior to separation of blood cells from plasma and subsequent freezing of the latter until the day of analysis. All samples were run in duplicate.

Assay precision tests yielded in our hands intra-assay coefficients of variation of 4·3% ($n=20, \bar{X}=110$ µg/l) and 3·8% ($n=20, \bar{X}=243{\cdot}7$ µg/l), and interassay coefficients of variation of 5·1% ($n=10, \bar{X}=87{\cdot}3$ µg/l) and 5·4% ($n=10, \bar{X}=202{\cdot}6$ µg/l). No modification of the plasma assay system was required for assessing the cyclosporin concentrations in aqueous humour samples.

Six months postoperatively the cyclosporin A 1% treatment was stopped, but the weekly examinations with the slit lamp were continued. When a rejection became clinically evident, the application of cyclosporin A 1% eye drops four times daily was resumed.

EXPERIMENT 2

Fourteen rabbits underwent a penetrating keratoplasty in the right eye in the same way as in the first experiment. At the same surgical session a comparable wound was made in the left eye—a perforating linear incision extending from limbus to limbus in the upper temporal quadrant; this was sutured with a running nylon 10-0 suture. The right eyes with the allografts were treated topically with drops of olive oil.

Cyclosporin A 1% in olive oil drops was instilled into the left eyes of seven randomly chosen rabbits. The remaining six rabbits received only olive oil drops in their left eye. All eye drops were applied five times daily. Slit lamp examination was carried out twice a week. Weekly blood samples were taken from an ear vein of five rabbits to determine the levels of cyclosporin A.[9]

Results

EXPERIMENT 1

Four weeks after keratoplasty the corneal allografts were still clear in all seven rabbits treated with cyclosporin A 1%. At that time, seven out of the eight control rabbits, had already rejected their graft; the last placebo graft was rejected on the 46th day, the median rejection time being 21·5 days. This justifies the conclusion that eye drops containing cyclosporin A 1% applied to the recipient eye five times daily for four weeks delays the rejection of corneal allografts in rabbits (Fisher's exact test, $0{\cdot}001 < p < 0{\cdot}01$).

Prolonged treatment was instituted in the seven rabbits whose eyes had received cyclosporin A 1% eye drops. Four rabbits were given four drops a day, and three rabbits were given two drops a day. Six rabbits retained a clear graft. One rabbit on a maintenance treatment of one drop twice daily rejected its graft on the 63rd day of the therapy

Table 1 *Concentrations of cyclosporin A (μg/l) in plasma and aqueous humour of both eyes after a six-month topical therapy with cyclosporin A 1% eye drops in the right grafted eye*

Rabbit	*Treatment frequency (drops a day)*	*Plasma*	*Right eye*	*Left eye*
2	4	136	95	166
5	4	233	121	144
7	4	60	91	93
10	4	151	168	182
18	4	187	254	172
8	2	119	162	105
16	2	113	118	54
Mean		141 286	144·143	130 857

Progressively increasing penetration of blood vessels arising from the limbus developed, associated with oedema of the graft. Once this graft was entirely cloudy and vascularised, the treatment was increased to one drop of cyclosporin A four times daily, which dose was maintained throughout the rest of the experiment. In a period of two months the vessels regressed and the oedema decreased, resulting in a clear graft with only barely visible ghost vessels. No other medication was used.

The concentrations of cyclosporin A in the plasma and the aqueous humour of both eyes are listed in Table 1. The samples of blood and aqueous humour were taken at the end of the six months of treatment with cyclosporin A 1% drops into the right, grafted eye. The cyclosporin A levels in the plasma and in the aqueous humour of the right and left eyes were similar, the difference not being significant (p>0·45 by the F test)

One rabbit (no. 2) died as a result of the general anaesthesia required to perform the paracentesis. In the remaining six rabbits, after discontinuation of the treatment, all grafts were rejected with a mean rejection time of 17 days. In one rabbit an epithelial rejection line was visible as early as the seventh day after cessation of the therapy. The clinical course of the rejection paralleled that of the control rabbits; there was ingrowth of blood vessels arising from the limbus associated with corneal oedema. An epithelial rejection line was frequently seen and often a quiescent anterior chamber with only a few cells.

Table 2 *Plasma concentrations of cyclosporin A (μg/l), during therapy with cyclosporin A 1% eye drops, five times a day in the left non-grafted eye*

Rabbit	*Postoperative day*			
	7	*10*	*14*	*21*
1	ND*	257	123	149
2	ND	261	84	51
11	138	113	80	128
13	159	117	64	90
14	139	64	29	71
Mean	145 3	162·4	76	97 8

*ND=not done

As soon as the rejection of the grafts was clinically evident, the topical treatment with cyclosporin A 1% into the recipient eye, one drop four times daily, was resumed. Gradually thereafter the vessels regressed, and the oedema of the graft decreased in a period of two to four weeks. However, no control group was available to determine the effect of the drug in this process.

EXPERIMENT 2

Cyclosporin A 1% or placebo eye drops were applied to the fellow eye, five times daily, in 14 grafted rabbits. One rabbit died as a result of the general anaesthesia; the other 13 rabbits all had a clear allograft in the right eye at the end of the first postoperative week. In seven rabbits cyclosporin A 1% in oil was applied to the left eye, one drop five times daily; all the right-eye allografts were rejected with a mean rejection time of 23·97 days. In the control group with placebo treatment the mean rejection time was 23·83 days. The plasma levels of cyclosporin A measured on different postoperative days are summarised in Table 2.

Discussion

The results of experiment 1[10] confirm earlier reports[5,6] that cyclosporin A 1% in oil eye drops applied to the recipient eye inhibit the rejection of corneal allografts in rabbits. A single retrobulbar injection of cyclosporin A[11] in oil likewise prolongs corneal allograft survival in rabbits. The minimum dosage required for complete immunosuppression appears to be one cyclosporin A 1% drop four or three times daily. We observed graft rejection in a rabbit on a maintenance therapy of two drops a day, and rejection occurred when the dosage was reduced to one drop daily in an analogous experiment.[6]

After discontinuation of the topical therapy all the grafts were rejected within four weeks, even though the animals had been treated for six months. This is contrary to Hunter and colleagues' findings that 44% of the grafts treated for three months with cyclosporin A 1% eye drops remained clear after the end of the treatment.[6] The most likely explanation of this difference is that we placed the allografts more closely to the limbus. In Hunter and colleagues'[6] experiment reactivation of the corneal blood vessels also resulted in typical corneal rejection in spite of the previous treatment with cyclosporin A. Although in our experiment no graft tolerance was induced, short term treatment with topical cyclosporin A could still be useful in clinical corneal transplantation. In the early postoperative period, when lymphocytes migrating in the traumatised eye have easy access to the cornea, the allograft might be protected by cyclosporin A. Later on, when the eye has become quiet, the graft might benefit from the relative immunological privilege of the cornea.

In our study, once the allograft rejection was established and the lymphocytes were accordingly sensitised to the foreign corneal tissue, the signs of rejection could again be suppressed by resuming the topical treatment with cyclosporin A 1% drops. This observation leads us to suggest that topically administered cyclosporin A exerts at least some influence on the efferent arch of the immunorejection. The respective parts played by the non-antigen-specific lymphotoxicity of cyclosporin A and the inhibition of the antigen-specific sensitisation of the T lymphocytes are still obscure.[11,12]

Considerable systemic absorption of topically administered cyclosporin A occurs in rabbits. We found plasma levels of cyclosporin A (Tables 1, 2) as high as those recommended for maximal graft survival in man. This raised the question whether in this model topically applied cyclosporin A might exert its immunosuppressive action by way of systemic absorption.

However, this was disproved by the second experiment. Cyclosporin A 1% eye drops applied five times daily to the fellow eye failed to inhibit rejection of the corneal allograft in the right eye. The mean rejection time in the control rabbits and the animals treated with cyclosporin A was the same, though plasma levels similar to those of the first experiment were observed. These elevated plasma concentrations apparently are too low to inhibit rejection of limbus—touching corneal allografts in rabbits.

Accordingly, the inhibition of the rejection of a corneal allograft by topically applied cyclosporin A 1% eye drops is due primarily to a local immunosuppressive effect in the cornea, limbus, conjunctiva, and possibly the sclera and regional lymph nodes. A contributory influence of the systemic concentrations (Table 1) is not excluded. The significance of the cyclosporin A levels found in the aqueous (Table 1) needs further study. During paracentesis in rabbits some contamination of the aqueous by plasma is hard to avoid. But even a very short disturbance of the blood-aqueous barrier cannot explain equal distribution of cyclosporin A in the plasma and the aqueous.

Our test animals did not manifest clinical signs of adverse general effects. In particular, no gastrointestinal toxicity[13] was observed. Because of the larger human body weight, it is to be expected that the use of cyclosporin A 1% eye drops in man will result in lower plasma levels, reducing the risk of systemic toxicity. Nevertheless we strongly recommend careful monitoring of cyclosporin A plasma concentrations in patients treated with cyclosporin A eye drops.

Sandoz Ltd kindly provided the cyclosporin A and the RIA kit components used in this study

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Microbial and immunological investigations of chronic non-ulcerative blepharitis and meibomianitis

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SUMMARY Concentrations of tear lysozyme, lactoferrin, ceruloplasmin, IgG, and IgA have been measured by enzyme linked immunosorbent assay (ELISA) in patients with chronic non-ulcerative blepharitis and meibomianitis at the same time as the lid and conjunctivae were cultured for bacteria and fungi by a semiquantitative method. A group of normal controls aged 20 to 80 were similarly sampled, when strains of *Staphylococcus epidermidis* from their eyes and the patients' eyes were biotyped according to Baird-Parker's scheme. 5% of blepharitis cases had increased numbers of *Staph. aureus* present on the lids, compared with only a scanty growth obtained from 5% of normals. 7% of blepharitis cases had increased numbers of *Staph. epidermidis* type VI (coagulase-negative, mannitol-fermenting) present compared with a scanty growth obtained from 6% of normals. Isolation rates of other types of *Staph. epidermidis* did not differ from those in normals; no types were associated with meibomianitis. Tear protein profiles were normal in most patients, and there was no increase in tear IgA or IgG, which is expected with chronic infection. Overall our evidence suggests that in 88% of cases these lid conditions have an inflammatory aetiology not associated with infection. Staphylococcal isolates often found in the eye usually represent a normal commensal rather than pathogenic flora.

Well recognised types of conjunctivitis and keratitis due to pathogenic bacteria such as *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella lacunata* have recently been reviewed.[1,2] However, the reasons why the normal skin flora might develop a pathological role in the causation of chronic infection in the external eye have not been considered recently. Before this can be done, we need to know precisely which organisms are involved. This is particularly relevant when the antibacterial effect of tear fluid is decreased or when the patient is immunocompromised. The possibility of local allergy developing in the external eye must also be considered.[3,4] This might arise as a result of increased numbers of an organism on the lid margin as a secondary response in a non-infective condition, or the organism might release its metabolic products to have a toxic effect on the conjunctiva.[5] These problems are highlighted by the clinical condition of chronic 'staphylococcal' blepharoconjunctivitis, in which there is doubt as to which type of staphylococcus (*Staph. aureus or epidermidis*) is involved, and as to whether the disease is due to a toxin, the bacterium, or an allergic response to it,[3,5] but is recognised clinically as 'staphylococcus sensitivity'.[6] The clinical diagnosis is further complicated when it is considered that the dry eye is described as being often infected with staphylococci (*Staph aureus* or *epidermidis*),[6] although these bacteria are also part of the commensal flora on the lid margin. In addition, laboratory tests for quantitative dryness of the eye have been most unsatisfactory in the past, relying erroneously on the Schirmer test when incorrect conclusions of 'dryness' have been drawn, since this test is only a crude measure of tear flow.

In order to investigate these problems quantitative bacterial culture has been performed and five tear proteins assayed in patients with chronic non-ulcerative blepharitis and meibomianitis. The isolates have been compared with culture results from 66 normal eyes. *Staph. epidermidis* biotypes have been identified and similarly compared with controls. Three tear proteins (lysozyme, lactoferrin, and ceruloplasmin) have been measured quanti-

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tatively by ELISA in samples of tear fluid, collected simultaneoulsy with the culture swabs, as well as immunoglobulins IgG and IgA to investigate whether there is an increase associated with infection. Tear protein analysis was undertaken to compare the tear protein profiles of these patients with those of normal controls of similar age and to differentiate those with profiles of 'questionably dry' or 'dry' eyes.

Although patients with chronic meibomianitis are generally considered to have an inflammatory condition, it was thought appropriate to investigate them similarly, in particular because of the copious amount of secretions that can flow from the meibomian glands on to the lid margin and conjunctiva. Investigations into the secretion and physiology of the meibomian glands have previously been performed by Linton *et al.*[7] and recently by Tiffany.[8]

Material and methods

The external eye was initially examined by biomicroscopic techniques, when patients were placed in clinical groups as defined below. Schirmer's test was carried out on the patients' eyes, after which tear samples were collected on to discs previously weighed accurately in tiny sealed polypropylene pots, specially manufactured for the transport of tear specimens,[9] when 150 µl of buffered saline was added to the disc in the bottle to form a tear eluate. They were transported to the laboratory, where they were held at −70°C until the tear proteins were assayed. The concentration of tear lysozyme, lactoferrin, and ceruloplasmin was assayed in each sample by an ELISA technique using direct binding of eluates or standards to polystyrene microtitre plates and a two-step indirect assay method with peroxidase-conjugated goat antirabbit IgG and rabbit sera specific for each protein.[10] Tear immunoglobulins were measured by ELISA with a direct method using polyvinyl plates and peroxidase-conjugated specific rabbit antihuman IgG or IgA. Techniques were developed to avoid cross reactions between each 'specific' antiserum and various other proteins, which were capable of causing gross inaccuracy before being investigated and removed[10]

After tear samples had been collected, both eyes of normal volunteers and patients were cultured for bacteria and fungi by a semiquantitative technique. Three wooden and two wire (pernasal) cotton-wool swabs were used for each eye. The lids were sampled first with the wooden swabs, which were each dipped into sterile distilled water. They were each rubbed along the lid from the lateral canthus to the punctum. The first swab was plated out on to a chocolate agar plate; the second was placed into a bijou bottle containing 0·5 ml distilled water, which preserves fungal spores; the third was placed into another bijou bottle which contained olive oil medium for culturing *Pityrosporum* sp. The conjunctivae were cultured after the lids with the wire swabs. They were similarly dipped into distilled water, but then rubbed along the conjunctiva from lateral canthus to punctum. The first was plated out on to a chocolate agar plate, and then placed into a new bijou bottle containing 0·5 ml distilled water; the second was placed into a new bijou bottle of olive oil medium. Plates were incubated at 37°C in CO_2 for 48 hours with chocolate agar, as it supports the growth of the normal commensal flora as well as the recognised pathogens. Fluid enrichment media were not used, as we wished to establish the predominant bacterial flora on a semiquantitative basis. All plates were inoculated in the clinic in a standard manner. The amount of growth for each culture was recorded as +/− (up to five colonies), + (up to 10 colonies), or ++ (10 to 100 colonies).

Bacterial colonies were identified by standard laboratory techniques.[11] Staphylococci were differentiated by the tube coagulase test into *Staph. aureus* or *epidermidis*, which were positive and negative respectively. Staphylococcal colonies isolated were further subcultured on mannitol salt (7·5%), agar (Oxoid CM85), and phenolphthalein phosphate 1% agar (Oxoid SR 31) to test them for mannitol fermentation, salt tolerance, and phosphatase production—simple Baird-Parker classification[12] for types I to VI (Table 1). For this study no distinction has been made between Baird-Parker types II and III, considered together as one group, and types IV and V, considered as the second group. Type VI strains, considered as the third 'epidermidis' group, were further typed biochemically and tested for their susceptibility to lysis by staphylococcal phages at the

Table 1 *Differentiation of* Staphylococcus aureus *and* Staph epidermidis *by simple Baird-Parker's scheme*

		Biotype (group)	*Tube coagulase*	*Phosphatase*	*Mannitol*
Staphylococcus aureus		I	+	+	+
Staphylococcus epidermidis		II/III	−	+	−
"	"	IV/V	−	−	−
"	"	VI	−	−	+

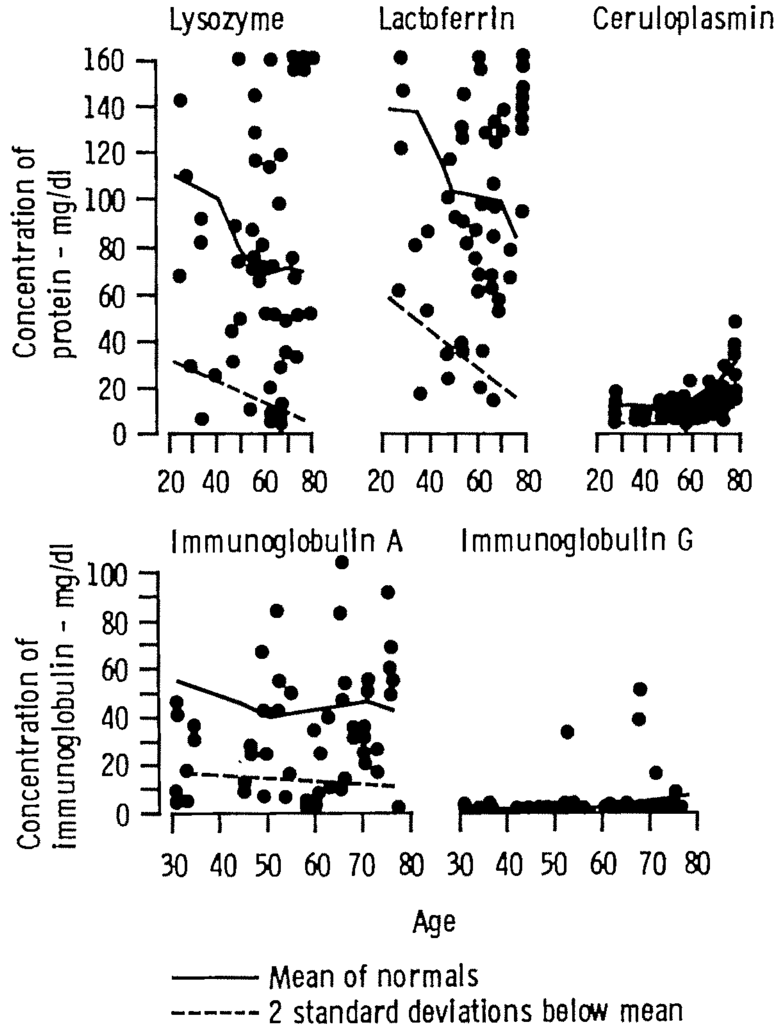

Fig 1 *Tear protein levels in chronic non-ulcerative blepharitis. (SI conversion mg/dl×0·01=g/L.)*

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The distilled water bijou bottles were kept at room temperature and subcultured within 24 hours onto Sabouraud's agar, both with and without chloramphenicol. Colonies were identified morphologically and microscopically with lactophenol blue stain. *Candida albicans* was confirmed by the 'germ tube' test. *Aspergillus* and *Penicillium* species were identified by their conidiospores and pigment production. The Olive oil media were incubated on receipt at 37°C, as they were suitable for both transport and culture. They were then incubated for seven days at 35°C. Presumptive identification of a *Pityrosporum* sp. was made by microscopical observation of their characteristic round bodies. This yeast-like fungus will grow only in media which contain fatty acids and does not grow on Sabouraud's agar alone. These two techniques, for fungal and pityrosporum culture, are qualitative and not quantitative. Because the isolation rate of fungi was expected to be low—approximately 3%[13]—a qualitative study seemed preferable.

PATIENTS

Both eyes of 33 normal volunteers were sampled by our modified Schirmer's test,[14] tear protein assay, and microbial culture. Both eyes of 26 patients with chronic non-ulcerative blepharitis were similarly sampled, as were 13 patients (26 eyes) with meibomianitis as well as 19 patients (38 eyes) in whom the clinical diagnosis of chronic blepharitis and possible dryness of the external eye was considered likely.

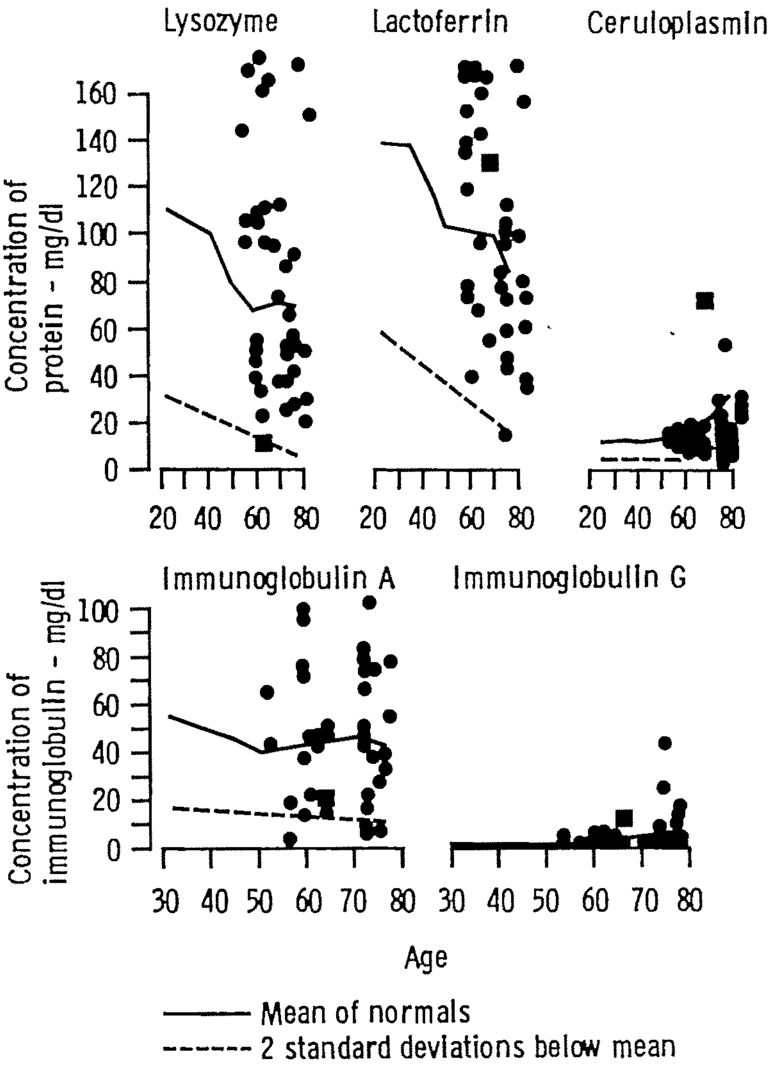

Fig. 2 *Tear protein levels in 'blepharitis and possible dryness.' (SI conversion: mg/dl×0·01=g/l.)*

A patient was deemed to have non-ulcerative blepharitis if the lid margins were crusted, scaley, or oily and the hair follicle bases were often infiltrated. Meibomianitis was described as present when the meibomian gland orifices were stenosed, infiltrated, and often pouting away from the lid margin They were often enlarged and visible beneath the conjunctiva. There was an associated frothy discharge present along the lid margins, which was often more apparent after the installation of rose Bengal. In both conditions associated tear film abnormalities included an uneven tear film, often filled with mucous threads, and debris with a decreased breakup time, and punctate erosions (staining with fluorescein) or keratopathy (staining with rose Bengal), particularly along the inferior conjunctiva and cornea adjacent to the lid margins If the tear film changes were marked, a dry eye state was said to exist, with a decreased marginal tear strip and precorneal tear film. Punctate keratopathy, as stained with rose Bengal, extended over all the epithelial surface in the interpalpebral fissure, particularly when the Schirmer test gave less than 10 mm wetting in five minutes.

A papillary conjunctival reaction was often present. In the suspected dry eye patient there was a variable punctate keratopathy over the conjunctiva and cornea in the interpalpebral fissure together with some or all of the tear film changes described above. Symptoms of non-ulcerative blepharitis included itching or burning of the lids and stinging eyes. If tear film changes coexisted, the symptoms included burning, gritty eyes and photophobia with 'reflex tearing.'

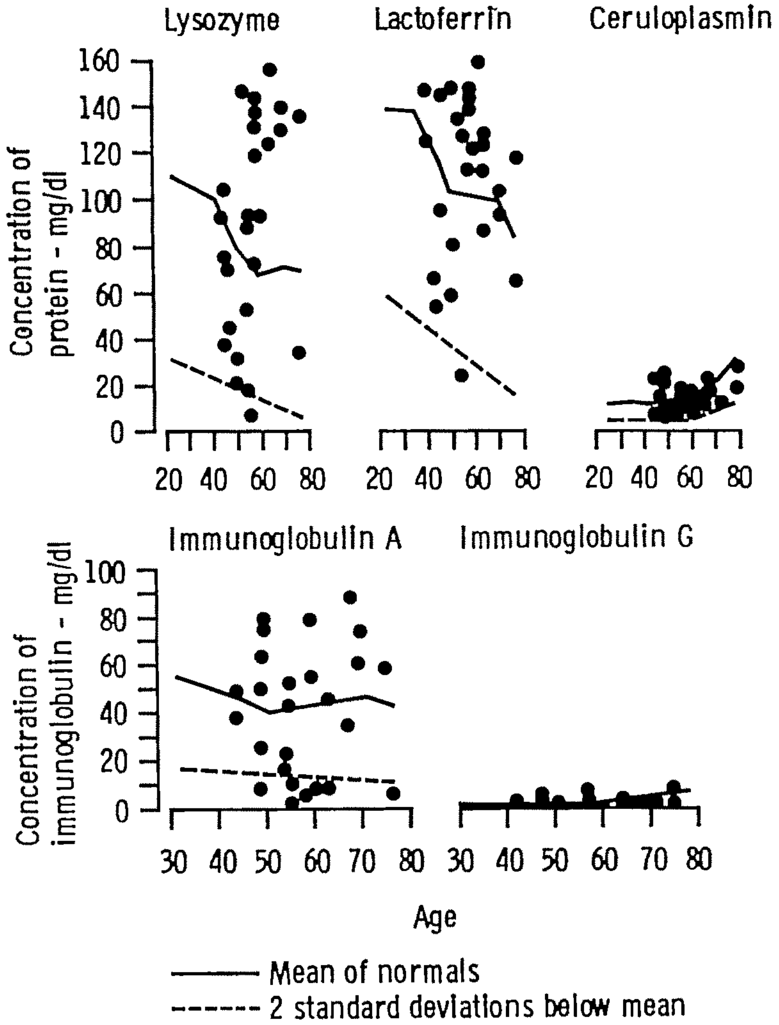

Fig. 3 *Tear protein levels in meibomianitis. (SI conversion: mg/dl×0·01=g/l.)*

Results

Concentrations of tear lysozyme, lactoferrin, ceruloplasmin and immunoglobulins IgG and IgA are given in Figs. 1 to 3 for each patient group studied. The mean normal values, and a 95% confidence limit of 2 standard deviations below the mean, were previously studied[15] and are shown in the figures, where the expected changes in concentration with age for each protein can be directly compared with the patients' levels. No significant differences were found between mean concentration values for each protein of the patient groups studied, and normal mean values as given However, five eyes in the chronic blepharitis group showed evidence of being 'questionably dry,'[14] with low levels of tear lysozyme and lactoferrin

Table 2 *Modified Schirmer test results for each patient group and normals*

Clinical group	*Mean age*	*Sex ratio (M/F)*	*Mean Schirmer result (mm)*	*Mean Schirmer value for age*[15]
Chronic non-ulcerative blepharitis	57	13/13	21	21
Blepharitis and possible dryness	69	2/17	13	17
Meibomianitis	57	8/5	22	21

There was no significant difference between the mean Schirmer results gained and the normal mean values expected for each age group

Table 3 *Qualitative bacteriology for each patient group and normals*

	Lid flora (% isolations in each group)			
	Normals eyes (*n*=66)	*Blepharitis* (*n*=52)	*Blepharitis and possible dryness* (*n*=38)	*Meibomianitis* (*n*=26)
Staph aureus (I)	5	8	9	12
—epidermidis (II/III)	48	42	34	40
—epidermidis (IV/V)	8	22	14	16
—epidermidis (VI)	6	10	12	0
Micrococcus	21	17	13	22
Streptococcus viridans	0	0	3	0
Diphtheroids	31	13	5	26
Neisseria sp.	3	0	0	0
Haemophilus sp	2	0	0	0
Moraxella sp	0	2	0	0
Coliforms	5	0	0	0
Pityrosporum sp	7·5	6·5	0	19*
No growth	17	6	8	13

*Significant difference from normals at 0·05 level

(shown in Fig. 1 lying greater than 2 standard deviations below the mean) but with normal levels of ceruloplasmin.

The mean ages, sex and Schirmer results are given in Table 2.

Table 3 gives the results of the various types of bacteria, including subtypes of *Staph. epidermidis*, isolated from each condition.

The results of conjunctival cultures were usually similar to those for the lid flora but occurred in a lower percentage of patients. In normal volunteers the conjunctivae were 'sterile' in only 17%, while conjunctival cultures yielded a different biotype of *Staph. epidermidis* from lid cultures in only 1%. Two different biotypes (groups) of *Staph. epidermidis* were simultaneously isolated from 8% of normals, 4% of patients with meibomianitis, and 21% of patients with blepharitis. Isolates of *Staph. epidermidis* biotype VI were later confirmed with further biochemical tests. They were divisible into three subtypes, but there was no association between any one subtype and the clinical group investigated. All isolates of biotype VI failed to show susceptibility to lysis by phage typing. There were no occasions when the conjunctival cultures gave a greater amount of growth than did the lid cultures, so it is considered that the conjunctival isolations made represented contamination of the conjunctiva by the lid margin flora.

Table 4 gives the quantitative bacteriology results

Table 4 *Quantitative bacteriology results for staphylococci isolated from lids and conjunctivae*

		% Isolations in each group							
		Normal eyes		*Blepharitis*		*Blepharitis and possible dryness*		*Meibomianitis*	
		Lid	*Conj*	*Lid*	*Conj*	*Lid*	*Conj.*	*Lid*	*Conj*
Staph aureus									
Biotype I	+/−	5	2	2	2	6	—	21	—
	+	—	—	4	4	—	3	—	—
	++	—	—	2	—	3	—	—	—
Staph epidermidis									
Biotype II/III	+/−	3	12	2	2	3	6	—	4
	+	35	20	36	32	28	11	40	20
	++	10	2	4	—	3	—	—	—
Biotype IV/V	+/−	—	5	2	—	—	3	—	4
	+	6	9	20	12	14	—	16	12
	++	2	—	—	—	—	—	—	—
Biotype VI	+/−	6	—	2	2	6	6	—	—
	+	—	2	8	2	3	—	—	—
	++	—	—	—	—	3	—	—	—

Table 5 *Mycology results for each patient group and normals*

Clinical Group	*Numbers with Pityrosporum sp isolated*	%	*Significance level*
Pityrosporum sp			
Normals	3/66	4·3	—
Blepharitis	5/52	9·6	Not significant
Blepharitis with possible dryness	1/38	2·6	Not significant
Meibomianitis	4/26	15·3	0·05
Other fungi			
Normals.	No fungi isolated		
Blepharitis.	Candida albicans (2 lids) Candida parapsilosis (lid + conjunctiva) Aspergillus flavus (lid)		
Meibomianitis	Rhizopus sp (lid)		

for staphylococci isolated from lids and conjunctivae.

Table 5 gives the results of fungi isolated from each condition.

Discussion

Using a semiquantitative culture method we found that 5% of blepharitis cases had increased numbers of *Staph. aureus* on the lids, while 7% had increased numbers of *Staph. epidermidis* type VI. Further, patients with blepharitis had a more frequent occurrence than normals (21% versus 8%) of two different biotypes of *Staph. epidermidis* being isolated simultaneously from the lids. We found similar numbers of *Staph. epidermidis* types II/III and IV/V in patients as in normals, and even found heavier growths in the normals than the patients, so that these organisms are unlikely pathogens. We failed to find a pathogenic bacterium in 88% of cases of blepharitis and all meibomianitis cases. It is thus quite likely that many reported isolations of staphylococci in association with blepharitis[1,16] or dry eyes[4] also represent commensal and not pathogenic flora, giving rise to much confusion in the literature and to misunderstanding of the pathogenesis of some external eye diseases. Our findings of increased numbers of coagulase-negative mannitol-fermenting staphylococci (*Staph. epidermidis* type VI) in some cases of blepharitis agree with those of Okumoto *et al.*[17]

Investigation of individual patients is best performed with the full quantitative culture techniques of conjunctival sponge discs[18] or soluble alginate swabs,[19] rather than ordinary swab techniques, when accurate enumeration can be attained of all the bacteria present, and the presence can be detected of increased numbers of a particular organism. Absolute numbers of bacteria have been established with the latter method for the normal eye.

Pityrosporum sp. has been isolated from cases of meibomianitis significantly more often, at the 0·05 level, than from normals. However, this fungus is present in large numbers on the normal scalp, and it has probably occurred more often because of copious meibomian secretions on the lid margin containing fatty acids, which support its growth. Both *Candida* and an *Aspergillus* sp. were isolated from patients with blepharitis on four occasions but not from normals. Whether they were present because of the inflammation on the lid margin is not clear, nor is it known whether they were present as transient flora. They were, however, isolated from only 4·4% of eyes with blepharitis.

Most cases (88%) of blepharitis and all of meibomianitis were uninfected and did not change tear immunoproteins as measured here. The effect on the tear film and association with debris in the film itself, such as punctate keratopathy of the conjunctiva, particularly along the lid margin, must be due to disturbance of the tear film components themselves, perhaps due to the excessive secretions from the lid margin. These effects include a disturbance of the tear film oily layer, the result of the blepharitis or meibomianitis leading to tear spillage from loss of the lid's tear-retaining properties, increased tear evaporation, and osmolarity. In the past, exotoxins from *Staph. epidermidis*[1] have been thought to play a part in producing the symptoms and signs that occur in these conditions but this now seems unlikely.

Comparison of tear protein profiles between each group and normals has failed to show a significant difference, though six eyes in the blepharitis group were 'questionably dry.'[14] The group of patients with 'blepharitis and possible dryness,' diagnosed on clinical examination alone, has been shown to have normal lacrimal gland function with normal tear lysozyme and lactoferrin levels, which demonstrates the difficulty of diagnosing early dryness of the external eye. Alternatively, localised dryness in the tear film is due to excess tear evaporation or mucin abnormality, with no alteration of the constituents of the watery layer of the tear film as sampled. The assays of IgG and IgA showed no increase, compared with normal controls, that would be expected if chronic infection is present.

McCulley *et al.*[20] have recently investigated the causes of blepharitis and suggested a classification including staphylococcal, seborrhoeic, mixed seborrhoeic/staphylococcal, mixed seborrhoeic/meibomian, and primary meibomianitis. They concluded that the role of staphylococci needs to be reassessed, in particular its pathogenicity and toxin production, which relates to studies performed in the 1930s and 1940s, as well as the effect of its release of lipases. Keith[21] has suggested that the condition is primarily seborrhoeic and that excess meibomian secretion is mainly responsible for the inflammation, although he grew staphylococci from one third of his cases—but did not compare them with controls. Baum[16] suggests that staphylococci represent the most important cause of blepharitis, though he reports successful treatment of some cases with topical steroids, which usually result in staphylococcal infections becoming worse. Cory *et al.*[22] investigated blepharitis in rosacea, including fatty acid secretion from the meibomian glands, but were unable to detect any differences compared with controls. There is a need to measure the different mediators of the inflammatory process in the tear film, and to identify the type of inflammation involved, as well as to consider the use of topical treatment with anti-inflammatory drugs other than steroids.

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Topographic visually evoked potentials induced by stereoptic stimulus

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SUMMARY Topographic processes of brain activity during stereopsis were investigated by means of two different principles, with a real stereo target and a computer stereogram. Use of either principle produced the same tendency: an electrically negative focus started from the central region of the scalp and moved to the parietal and occipital regions. These flows of excitation were seen during a period of 90 to 170 ms. The difference between these two stimulus represented a return of the negative focus from the occipital pole to the parietal region in the real stereo target and a spread of the negative focus to the temporal region in the computer stereogram. Since monocular viewing of a real stereo target produces a similar visually evoked potentials wave form but with less intensity, the negative focus in binocular viewing may be due to the enhancement of binocular cells and disparity sensitive neurons in a wide area of the brain cortex. Thus stereoptic brain responses start from the central and parietal regions and move to the occipital region, making a flow of excitation.

Brain activity during a stereoptic vision was studied by means of the newly developed dynamic topography[1 2] of visually evoked potentials (VEP). For stereoptic stimulation two different stimulators, a real stereo target and a computer stereogram, were employed and the results were compared.

In the previous studies on stereoptic VEP[3-6] the main emphasis of discussion was VEP enhanced by a stereoptic target. However, the present paper reports an investigation of the topographic process of brain activity during stereopsis by means of the dynamic topography developed by Lehmann *et al.*[1] and Tsutsui *et al.*[2]

Methods and materials

Two types of stereo stimulators were used. The first was the combination of a liquid crystal shutter and a real stereo target which has been previously reported.[4 7] Electric liquid crystal shutters were used as a visual stimulator with a computer trigger. The stimulus consisted of the appearance of a target for 1000 ms and its disappearance for 1000 ms. The time needed for the shutter opening was 1 ms and for its closing 4 ms. VEPs were recorded during the target's appearance for 512 ms. Styrofoam blocks of random height, with a surface measurement of 12×12 mm, were fixed on the inside of a transparent plastic perimeter with a diameter of 60 cm. The total number of blocks was 169, these occupying 20° of the central field. The average depth of the uneven surface was 4.5 cm and the distance from the subject's eyes was about 45 cm.

The second stereo stimulator was a red-green stereogram on the cathode ray tube (13 inches (33 cm)) of a personal computer (NEC PC-8800). The stereogram consisted of three simple rectangles (4·5×9·0 cm, 3·2×6·4 cm, 2·3×4·6 cm, with visual angles of 191′×381′, 136′×271′, 98′×195′, respectively) with disparities of 42′, 31′, and 19′ when the shift appeared. Using red-green glasses, the subjects were seated 50 cm from the CRT.

The computer triggered a shift of rectangles to produce depth in the front of the background. The modes of depth stimuli appeared for 1300 ms and disappeared for 1300 ms, but VEPs were recorded for only 512 ms during the appearance time.

The computer-triggered shift of disparity induced a depth perception in front of the background, while the disappearance of disparity showed loss of depth perception. For fixation the subjects were advised to look at the area displaying a disparity, since pinpoint fixation lost the depth sensation. Eye movement was always monitored from electrodes Fp_1 and Fp_2 to

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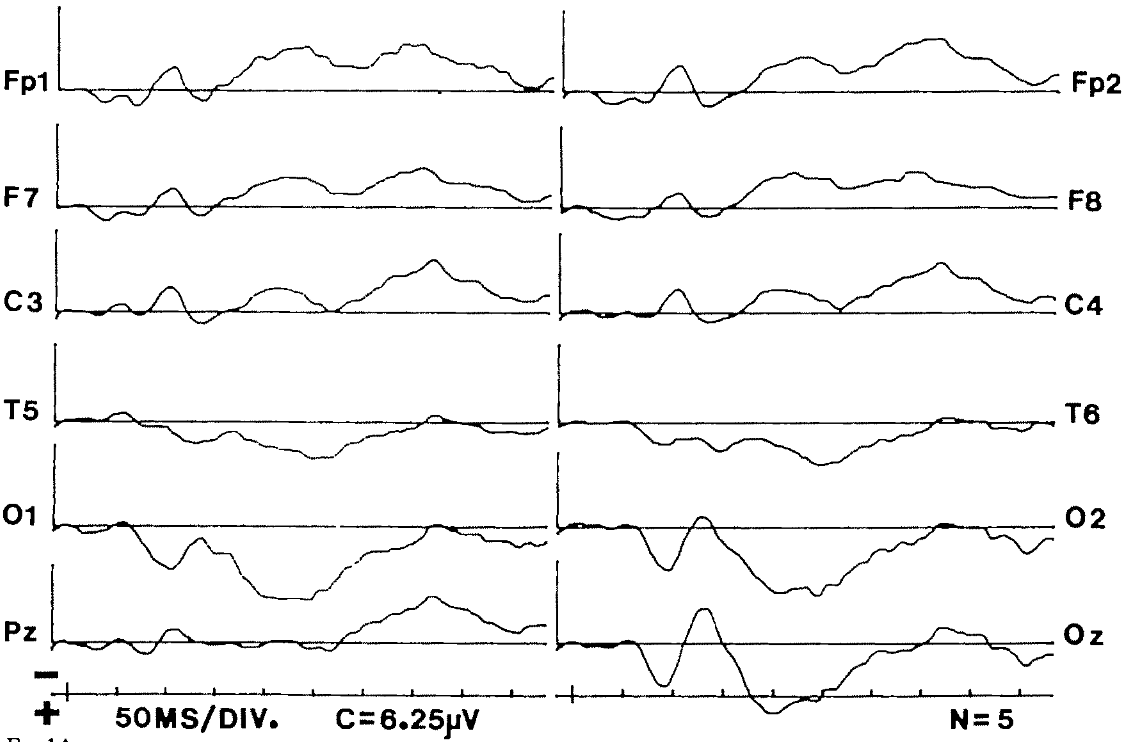

Fig 1A

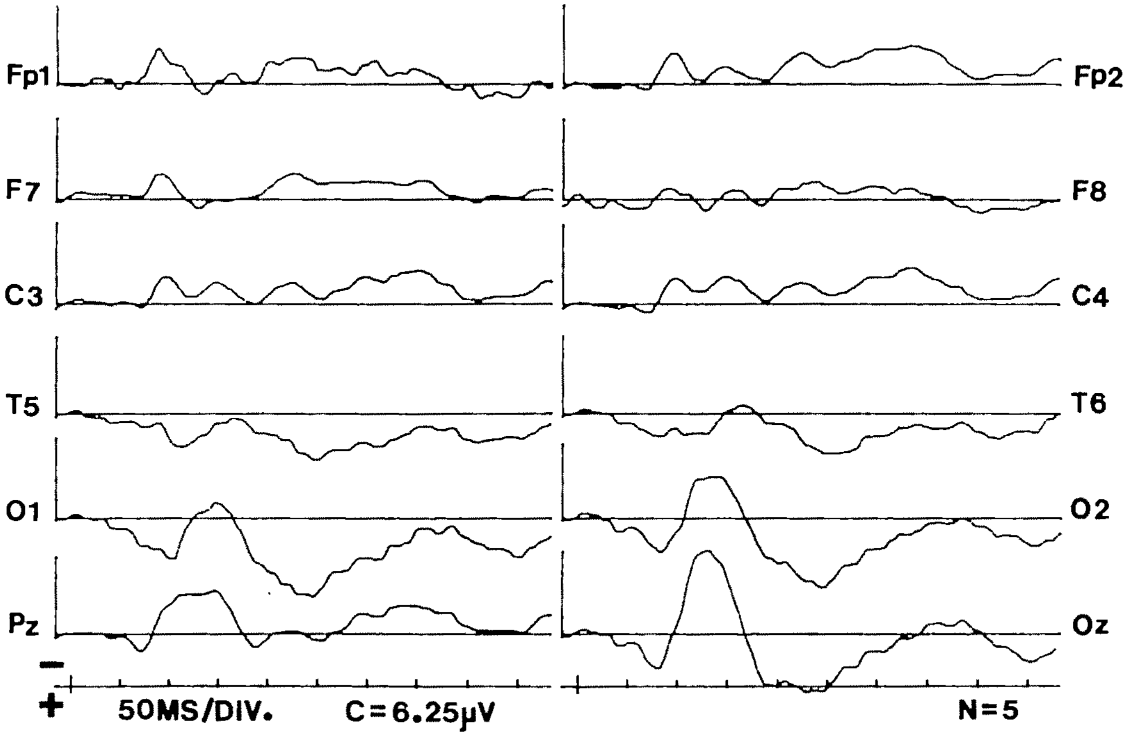

Fig. 1B

Fig 1 *VEPs induced by real stereo target. Grand averaged data from five subjects by monocular* (A) *and binocular* (B) *stimulation.*

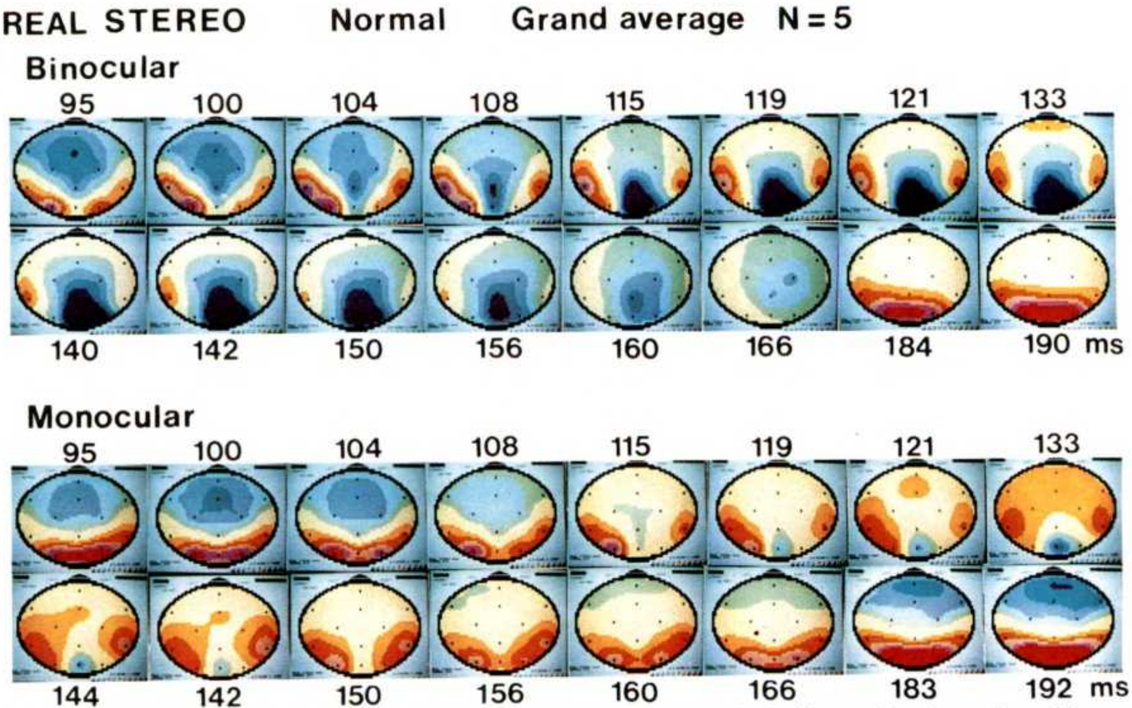

Fig. 2 *Grand averaged dynamic topograms of VEPs (n=5) in real stereo target. Red-yellow: positive charge. Green-blue: negative charge. Colour step 0·5 μV.*

avoid contamination of the electro-oculograph (EOG). Blinks were inhibited during the appearance of disparity and permitted during its disappearance.

Recordings were made from 12 electrodes located at Fp$_1$, Fp$_2$, Fz, F$_7$, F$_8$, C$_3$, C$_4$, T$_7$, T$_8$, Pz, O$_1$, and O$_2$ according to the international 10-20 method. The reference electrodes were attached at A$_1$ and A$_2$ and the ground was placed on the forehead. The band-pass filter was set from 0·53 to 60 Hz. Electro-encephalographs (EEGs) were recorded by a paper recorder and a 16-channel data recorder (TEAC Co., Tokyo, SR-70) during experiments. Both stimulators produced an average of 50 responses. In order to make an animated movie, the whole process of VEP, completed in about 300 ms, was displayed on the CRT of a BEAM (brain electric activity map) computer (EEG Topography System 500, Sanei Sokki, Tokyo) at 1 ms intervals. Evoked potentials at each electrode were also recorded by XY recorder.

Ten normal subjects with a stereoacuity of 40 seconds (5 males and 5 females, aged 20 to 60) were studied and their VEPs were superimposed. For making a dynamic topogram five cases showing a high reproducibility and few electric artefacts were selected for the grand average presented in this paper.

Results

REAL STEREO TARGET

Major differences in the wave forms of binocular and monocular stimulation were a remarkable enhancement of the N$_{150}$ component at Oz and a negative deflection (−3·4 μV) from 90 to 175 ms at Pz during binocular viewing (Figs. 1A, B). These peculiarities were clearly demonstrated in the dynamic topograms recorded from 95 ms of binocular viewing. A large negative focus expanded from the Fz and moved to Cz (at 100 ms), Pz (at 108 ms), and Oz (at 119 ms), continuously, with an amoeba-like movement (Fig. 2, binocular). The negative focus at the occipital pole was reduced in intensity at one time, but its return from the occipital pole to the parietal region was recognised during the period from 136 to 160 ms.

During monocular stimulation, however, the negative focus from 90 to 108 ms appeared at the Fz and Cz (at 108 ms), and less intensive development occurred in the parieto-occipital area (Fig. 2, monocular). The later movement of focus which was recognised in the binocular viewing did not appear. The negative focus at the parietal centre (Pz) was peculiar in the binocular viewing, and the increased

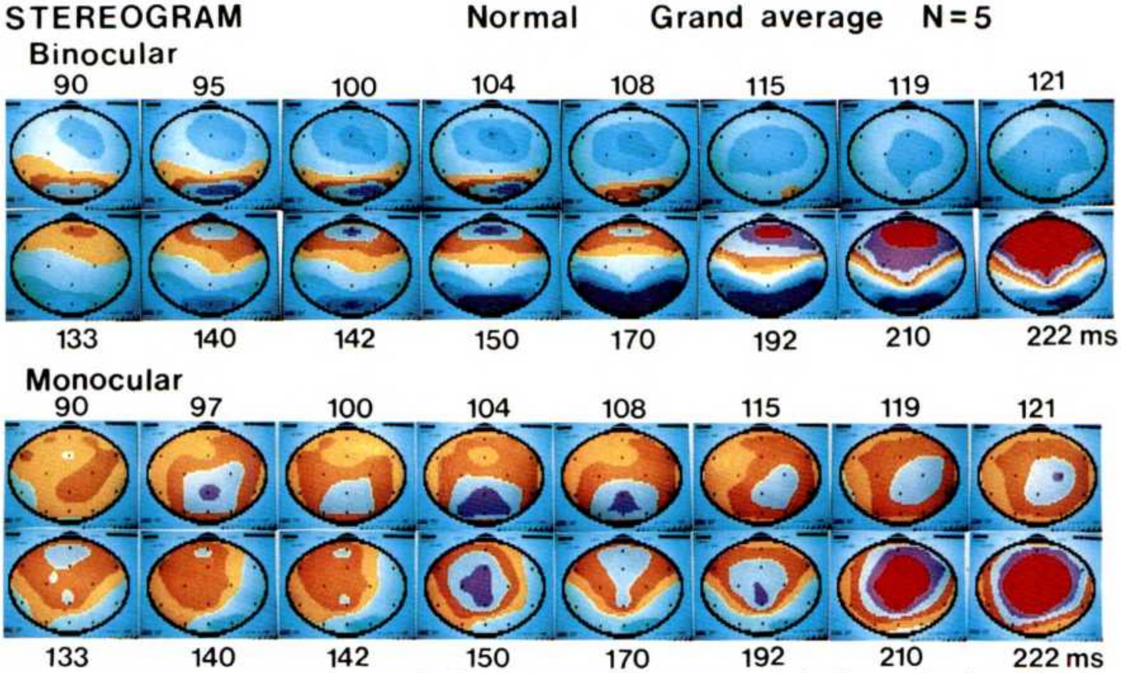

Fig. 3. *Grand averaged dynamic topograms of VEPs (n=5) in computer stereogram. Red-yellow: positive charge. Green-blue: negative charge. Colour step 0·3μV.*

negativity at the occipital centre (Oz) developed the enhancement of binocular effect. The amplitude of N_{150} in monocular viewing was −2·8 μV and in binocular one was −6·6 μV; thus the binocular effect was 235%. After the parieto-occipital negativity, positive focus appeared in both monocular and binocular viewing for the same period and to the same extent in the occipital region.

COMPUTER STEREOGRAM

The dynamic topogram (Fig. 3) was displayed from the grand average of five cases whose 12 channel VEPs are illustrated in Figs. 4A, B. From 90 ms after the appearance of depth a positive discharge appeared in the occipital region and continued up to 108 ms. This response was obtained through both monocular and binocular stimulation and was interpreted as the P_{100} of conventional VEP. Binocular stimuli, however, showed a peculiar course of responses, that is, a negative focus (−0·9 μV, 90 ms) appeared from the centroparietal region, moving to the occipital pole with an amoeba-like movement. The maximum occipital focus (−4·5 μV) was seen from 170 to 192 ms and disappeared after 222 ms. This peculiar course was not produced by the monocular stimuli.

Discussion

For studies on the topographic process of stereopsis in the brain two different stereo stimulators—the real stereo target and the computer stereogram—were used, and results were compared to find out the similarity in stereoptic brain activity.

Both stimulators showed the same tendency: the appearance of a negative focus in the centroparietal region from 90 to 170 ms after the appearance of depth. The flow of negative focus started from the central portion and moved to the occipital pole with the use of either stimulus. The only difference noted between the effects of the two stimulators was a return of negative focus from the occipital pole to the parietal region with the real stereo target and a spread of negative focus to the temporal region with the computer stereogram.

The flow of negative focus suggested that a relatively wide area of the brain contributes to the establishment of stereopsis. Fusion, convergence, and small eye drift might be necessary to achieve stereopsis. In my present assessment this negative focus is not specific for stereopsis but, rather, it may be the enhancement of the monocular response. This assessment is supported by the observation of a weak

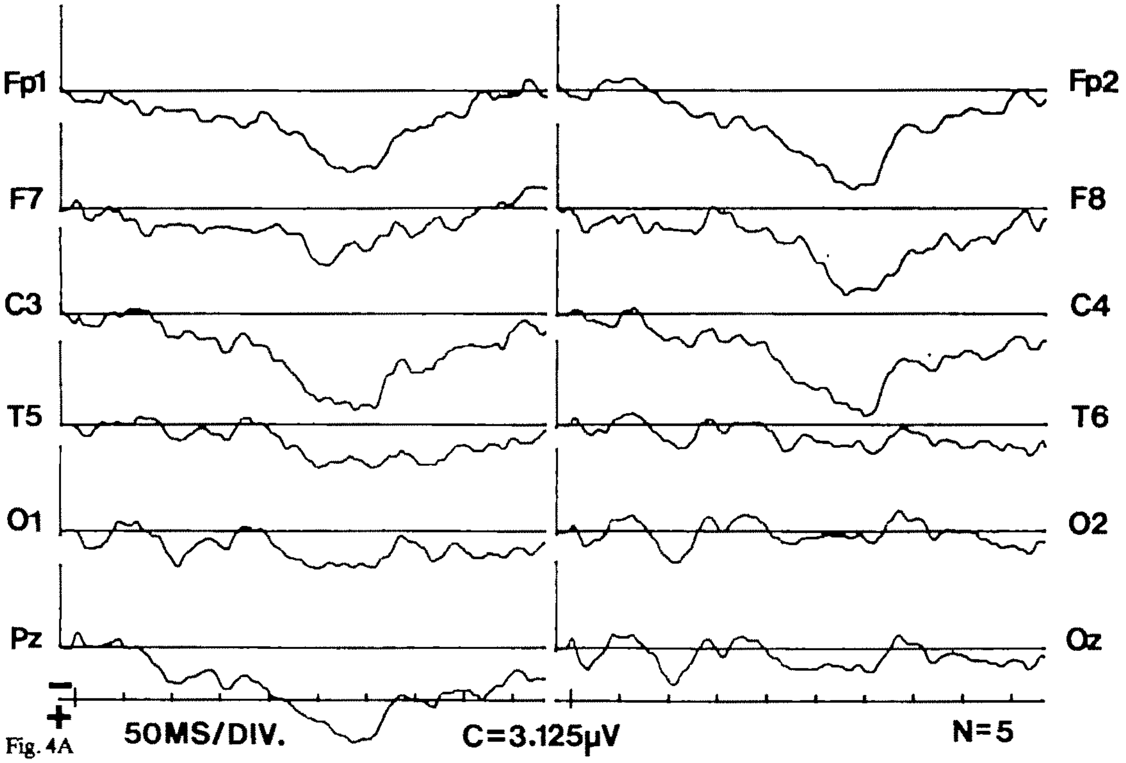

Fig. 4A

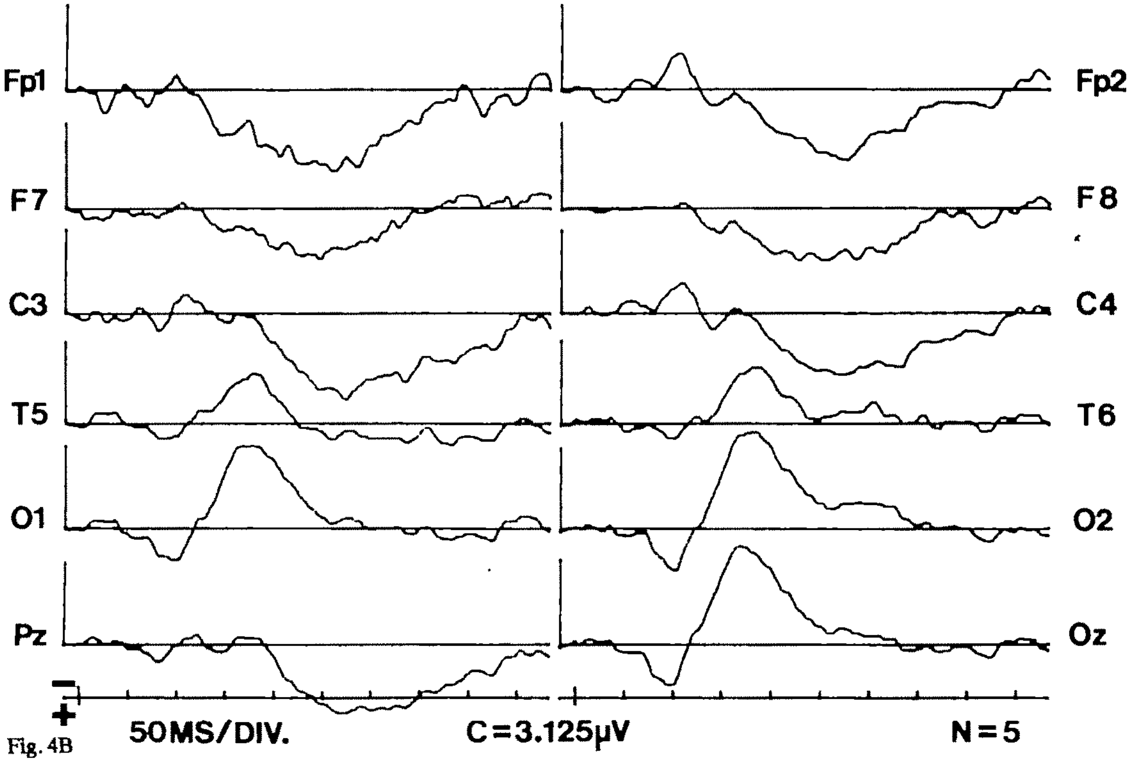

Fig. 4B

Fig. 4 *VEPs induced by computer stereogram. Grand averaged data from five subjects by monocular* (A) *and binocular* (B) *stimulation.*

negative focus which appeared in the middle central scalp from 90 to 110 ms even with the monocular cue of the real stereo target. But the late response in the area from the parietal to the occipital pole was much stronger with binocular stimulation than with monocular. This phenomenon may be due to the enhanced response of binocular cells, which are also sensitive to monocular stimulation to a less extent. Poggio and Fischer[9] reported that in monkeys nearly all cortical neurons in areas 17 and 18 were binocular neurons, but monocular stimulation with some ocular balance could also occur.

The binocular effect of VEP reported previously depends on the negative component at 150 ms (N_{150}) in the parietal and occipital areas. In our previous studies on the stereoptic stimulator using the binocular liquid crystal shutters and a real stereo target[2,4,7,8] the binocular effect of VEP was parallel to the subjective stereopsis in normal and strabismic patients. In the reports of most other authors[3,5,6] studying the stereoptic VEP a random dot stereogram was employed. As stated earlier, the stereogram used in this investigation did not employ random dots; linear rectangles with disparities were displayed. In the Julesz's type random dot stereogram the appearance of checkerboard-like rectangles might induce a pattern VEP combined with depth discrimination.

As regards brain activity during stereopsis, Herpers *et al.*[6] emphasised that the negative component was localised in the central and parietal regions during the period from 150 to 250 ms. Although the peak time of the negative component obtained in this study showed little difference from that of Herpers *et al.*, the same tendency of response was clearly demonstrated here. Herpers *et al.* emphasised that the stereoptic brain response was localised in the central and parietal region and was not generated in the occipital region. In this study, however, the occipital region showed a negative potential in the late stage. The meaning of the centro-parieto-occipital travel of brain activity has not clearly been interpreted, but it suggests that many steps of neural function may produce stereopsis.

As regards the cerebral centre of stereopsis, no hemisphere preference was found in this study. This result is in agreement with the report of Lehmann and Julesz.[3] As to the higher integration potentials, such as vertex potentials of P_{200} and event-related potential P_{300}, the negative component in stereopsis was easily differentiated.

In conclusion, our study shows that the stereoptic response in the brain starts from the central and parietal regions and moves to the occipital region, making a flow of excitation.

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Progressive retinal atrophy in the Abyssinian cat: studies of the DC-recorded electroretinogram and the standing potential of the eye

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SUMMARY DC-recorded electroretinography (ERG) and direct recordings of the standing potential (SP) were performed on a group of normal cats and Abyssinian cats affected by a hereditary retinal degenerative disease with similarities to human retinitis pigmentosa. A significant reduction of a- and b-wave amplitudes was found at an early stage of disease at a time when there were no major alterations in the c-wave and SP. At later stages both the c-wave and the SP oscillations were significantly reduced or absent. These findings indicate a primary photoreceptor disorder. Threshold studies for the scotopic b-wave showed a loss of retinal sensitivity early in the disease at a time when 30 Hz flicker responses were normal, which could indicate an earlier involvement of the rods than of the cones. There were no major alterations in the timing of the ERG in the affected animals tested.

Progressive retinal atrophy (PRA), a slowly progressive retinal degenerative disease, has been described in Abyssinian cats.[1-3] In a study of 17 parental matings the disease was found to be transmitted by a simple recessive gene.[4] In affected cats a bilateral retinopathy is usually ophthalmoscopically evident between 1½ and two years and progresses to cause blindness in another two to three years. In the early stages of the disease the photoreceptor layer in the midperipheral and peripheral region is more severely affected than in the posterior pole. The disease progresses and the retinal degeneration becomes generalised. It was suggested that PRA in the Abyssinian cat is a heritable photoreceptor degenerative disorder with a fairly slow rate of progression.[3]

The present studies were performed to characterise the disease further, to correlate the electrophysiological changes with the disease stage as seen by ophthalmoscopy, and to study the development and progression of electrophysiological abnormalities during the course of the disease. A DC-recorded electroretinography (DC-ERG) technique was used which allows stable and reproducible recordings of the a-, b-, and c-waves as well as direct recordings of the standing potential (SP) of the eye in a clinical situation.

Materials and methods

Electrophysiological studies were performed in six normal control and seven affected Abyssinian cats (Table 1). Both affected and control cats were household animals and not maintained under standard laboratory animal conditions.

The cats were premedicated with atropine and zylazine (Rompun). General anaesthesia was induced with pentobarbital and maintained with the same substance diluted in Ringer's solution delivered through an infusion pump (infusion dose and rate: 3·5 mg/kg/h). The cats were intubated and their pulse, respiratory rate, and body temperature monitored continuously during the three hours of the procedure. The pupils were dilated with 10% phenylephrine and 1% atropine. Dark adaptation time was 45 minutes. DC recordings of the dark adapted ERG and the SP of the eye were studied. The technique has been described previously in more detail.[5,6] In summary, a suction contact lens was applied to each eye and a reference chamber placed nasal to the occiput, all of which were connected by saline-agar bridges to matched calomel half-cells,

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low-drift DC amplifiers (300 Hz cut-off, 12 dB/octave), a desk top computer system (Hewlett Packard 9826, 9895A, 7225B, 9876A, and 6940B, USA), and analogue tape recorder and a chart recorder. The results of the ERG studies were plotted and stored on floppy discs for later analysis. The contact lenses, which were centred on the visual axis, had a slightly opaque surface to assure an even illumination of the retina. The stimulus light was produced by a 150 W xenon lamp and was guided to the eyes by quartz fibre optics ending 5 cm in front of each lens.

The a-, b-, and c-waves of the ERG were recorded in response to 1- second white light stimuli. Light intensities were varied in 0·5 log unit steps by using neutral density filters (Balzer) from slightly below the normal b-wave threshold, set at 25 µV, to about 7 log relative units above the normal b-wave threshold. Stimulus intervals were 60–180 seconds depending on light intensity. Threshold determinations for the b-wave were followed by amplitude and implicit time studies for the a-, b-, and c-waves over the intensity range. The amplitude of the b-wave was measured from the trough of the a-wave, whereas that of the a- and c-waves was measured from the isoelectric line. Implicit time was measured from stimulus onset to the peak of the individual responses. Flicker studies at 30 Hz were performed with a high intensity of white light (Clinical photic stimulator, Specialized Laboratory Equipment, UK, setting 4), clearly within the photopic range. Following dark adaptation the SP was recorded after turning on a continuous white light stimulus (5·67 log relative units above b-wave threshold) for 30 minutes. The maximum amplitude of the light rise was measured from the isoelectric line, and the implicit time from stimulus onset to the peak of the light rise.

DC-ERG recordings were performed on six of the control cats (N1–N6) and flicker and SP recordings on five (N1, N2, N4–N6). Electroretinographic flicker, and SP studies were carried out on all affected

Table 1 *Animals included in the study*

Cat no	*Breed*	*Sex*	*Age*	*Fundus/stage**
Control				
N1	Domestic short-haired	F	1 yr	Normal
N2	Abyssinian cross	M	2 yr	"
N3	Abyssinian cross	F	2 yr	"
N4	Abyssinian (Somali)	F	6 mo	"
N5	Abyssinian	F	4 yr	"
N6	Abyssinian	M	5 yr	"
Affected				
A1	Abyssinian	M	6 mo	Stage 1
A2	"	F	6 mo	Stage 1
A3	"	F	1½ yr	Stage 2
A4	"	F	3 yr	Stage 2
A5	"	F	3 yr	Stage 3
A6	"	F	4 yr	Stage 4
A7	"	F	5 yr	Stage 3

*Stage of disease·

Stage 1 (stage of suspected disease). slight discoloration mainly near the disc.

Stage 2 (stage of early disease). discoloration and slight vessel attenuation most apparent in peripheral and/or midperipheral tapetal fundus

Stage 3 (stage of moderately advanced disease) distinct colour change in entire tapetal fundus and marked vessel attenuation

Stage 4 (advanced stage of disease) generalised hyperreflectivity of tapetal fundus, decoloration and sometimes hyperpigmentation of non-tapetal fundus, vessels extremely attenuated or invisible

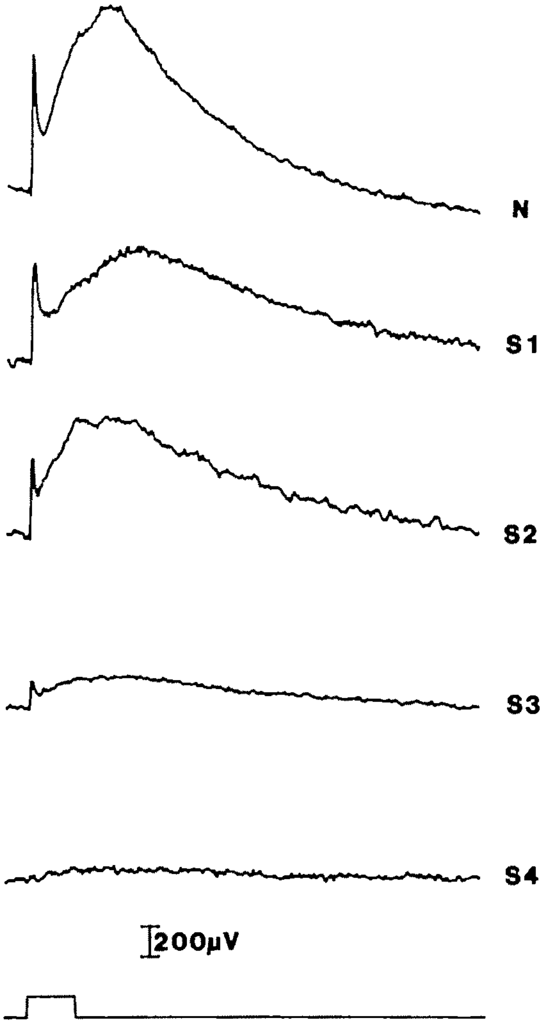

Fig. 1 *Dark adapted electroretinogram of a normal Abyssinian (N) and of four affected cats at stages 1–4 (S1–S4). One second white light stimulus (5·17 log relative units above b-wave threshold) indicated below recordings. Stimulus conditions identical for all recordings.*

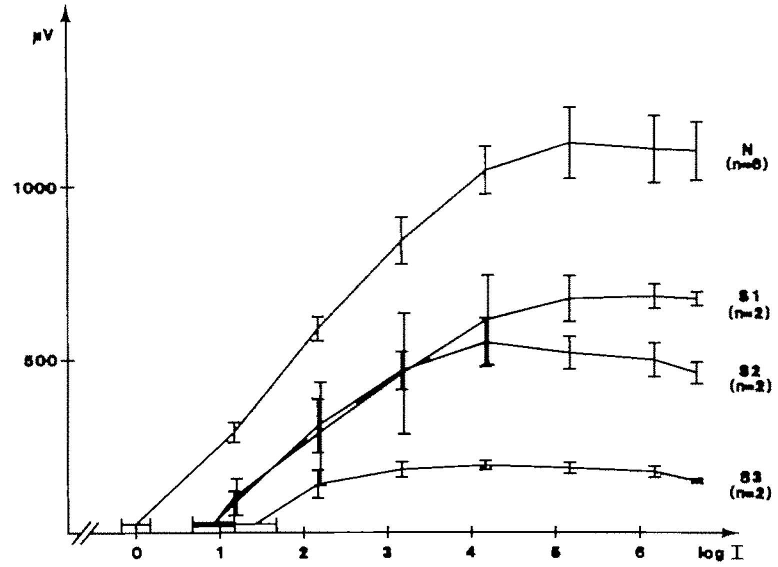

Fig. 2 Log intensity-amplitude (mean and SEM) relationship for the dark adapted b-wave in normal cats and in affected Abyssinians at stages 1–3 (S1–S3). Thresholds (mean and SEM) are shown parallel to the abscissa n=Number of cats in each group

animals (A1–A7). For flicker and SP recordings A1 was used twice—at stages 1 and 2. Data were statistically analysed by the one-tailed Student's t test.

Results

ERG: THRESHOLD AND AMPLITUDE

Fig. 1 shows representative recordings from normal and affected cats at different stages of disease.

Fig. 2 illustrates the dark adapted intensity-amplitude relationship for the b-wave in normal and affected cats at different stages of the disease. In normal cats the amplitude of the b-wave was linearly related to the logarithm of the stimulus at low light intensities. At higher intensities the relationship became non-linear. The threshold distribution for normal cats was −0·17 log relative units (SEM), with the use of a 25 µV b-wave criterion response for threshold. In the affected group (stages 1, 2, and 3) there was an elevation of thresholds which was highly significant ($p<0{\cdot}0005$). Even at stage 1 the difference was significant ($p<0{\cdot}02$) in comparison with the controls. The maximum b-wave amplitude for the intensities used was 1127—103 µV (SEM) for the normal group of cats, while for the affected group (stages 1, 2, and 3) there was a highly significant reduction ($p<0{\cdot}0005$), already noticeable at stage 1 ($p<0{\cdot}05$). The reduction in maximum amplitudes corresponded well with the stage of disease: 40% at stage 1, 51% at stage 2, and 83% at stage 3. In one cat with advanced PRA (stage 4) there was no recordable ERG (not included in the calculations or in the figure).

The dark adapted intensity-response relationship for the a-wave is illustrated in Fig. 3. In normal cats there was a linear increase in amplitudes at higher light intensities, and the maximum amplitude for the intensities used was 283±39 µV (SEM). In the affected group (stages 1, 2, and 3) the maximum amplitudes were significantly lower ($p<0{\cdot}05$). Again, there was a certain relationship between the maximum amplitudes found and the stage of disease. At stages 1, 2, and 3 the average reduction was 47%, 55%, and 87%, respectively.

Fig. 4 demonstrates the dark adapted intensity-reponse relationship for the c-wave in normal and affected cats. The maximum c-wave amplitude for normal cats was 1020±122 µV (SEM). At stages 1 and 2 the reduction in maximum amplitudes was not significant ($p<0{\cdot}25$ for stage 2); at stage 2 the c-wave amplitude was about 21% of normal. At stage 3, however, there was a significant difference in maximum amplitudes between affected and control animals ($p<0{\cdot}01$).

ERG: TIME COURSE

In both controls and affected cats there was a reduction in implicit time for the a- and b-waves, while for the c-wave there was an increase in implicit time, as higher light intensities were used. There was no major difference in b-wave implicit time between affected cats and controls during scotopic conditions with dim light stimuli. Only at one high light intensity

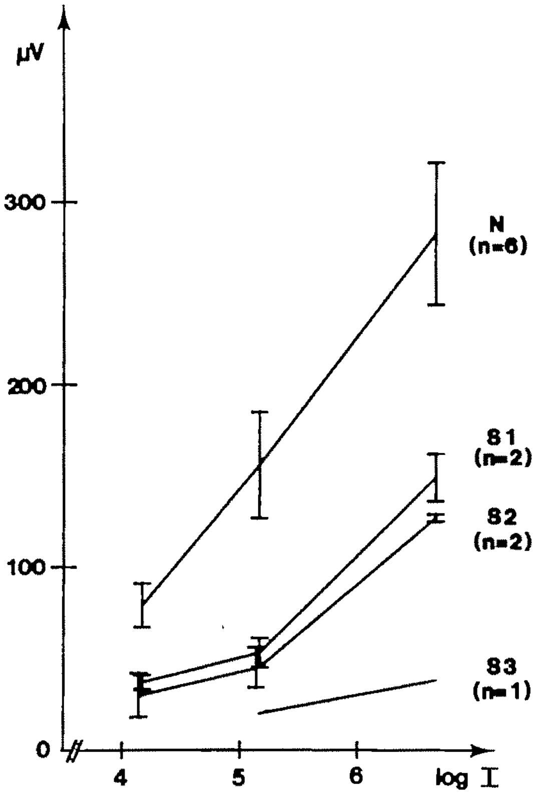

Fig. 3 *Log intensity-amplitude (mean and SEM) relationship for the dark adapted a-wave in normal cats and affected Abyssinians at stages 1–3 (S1–S3). n=Number of cats in each group.*

(5·17 log relative units above b-wave threshold) was a significant difference in b-wave implicit time found ($p<0{\cdot}01$). For the a- and c-waves the implicit times were similar in affected cats and controls at all light intensities used in the study.

ERG: FLICKER

In control cats the mean b-wave amplitude for 30 Hz flicker was 16±1·0 µV (SEM), while the mean implicit time was 29±1·0 ms (SEM). In affected animals the five recordings from stages 1 and 2 showed a mean amplitude of 14±26 µV (SEM) and a mean implicit time of 30·4±0·7 ms (SEM). These figures were not significantly different from those of the normal cats. There was no recordable flicker responses in the other affected animals.

SP

Fig. 5 demonstrates representative SP recordings from a control cat and two affected animals at stages 1 and 2. In normal cats a light rise with a distinct peak was seen with a mean amplitude of 2·5±1·5 mV (SEM) and a mean implicit time of 5·3±1·4 min. (SEM). Further, a less prominent second oscillation was seen in some of the normal cats at about 26 minutes. For affected cats the five recordings at stages 1 and 2 showed a mean amplitude of 2·7±0·5 mV (SEM) and a mean implicit time of 6·5±0·5 min (SEM). These figures do not differ significantly from those of the normal cats. At stages 3 and 4 no light rise was seen.

Discussion

The successive reduction mainly of a- and b-wave amplitudes indicates that the retinal degeneration found in this strain of Abyssinian cats is primarily a photoreceptor disorder. Threshold studies for the dark adapted b-wave showed that there was a loss in retinal sensitivity early in the disease process, indicating an early involvement of the rod system. The cone system seemed, however, to be spared in early cases, as seen by a normal 30 Hz flicker response. For the c-wave and SP there were no major alterations at stages 1 and 2, which showed a good function of the pigment epithelium in early cases. With progression of disease, when there was a substantial reduction in a- and b-wave amplitudes, there was also a significant reduction of the c-wave amplitude and an abnormal SP response, which possibly might indicate an involvement of the pigment epithelium as well. However, since both the c-wave and the SP reflect an

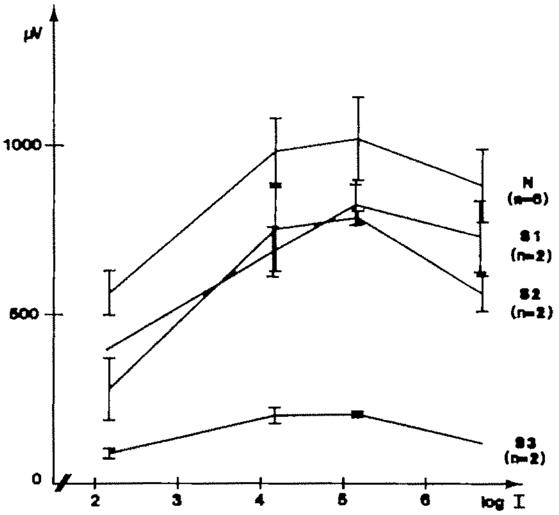

Fig. 4 *Log intensity-amplitude (mean and SEM) relationship for the dark adapted c-wave in normal cats and affected Abyssinians at stages 1–3 (S1–S3). n=Number of cats in each group. At 2·17 log I units for S1 and at 6·67 log I units for S3 the results of one cat were recorded.*

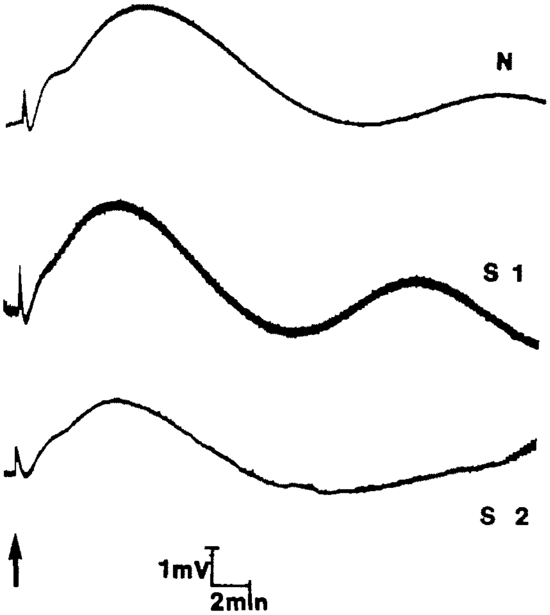

Fig. 5 *Representative SP recordings of a normal Abyssinian cat (N) and of affected animals at stages 1 and 2 (S1–S2). The recordings were performed, following dark adaptation, after turning on a continuous white light stimulus (5·67 log relative units above b-wave threshold) for 30 minutes.*

interaction between neuroretina and pigment epithelium,[5-8] these alterations could be mainly secondary to the photoreceptor dysfunction.

Results of histopathological studies presented previously,[3] support the electrophysiological findings in this study. Light microscopy at the early stage of disease showed alterations in the photoreceptor layer, while other parts of the retina, including the pigment epithelium, appeared normal. The midperipheral and/or peripheral retina were most severely affected; they showed a reduced outer nuclear layer and disorganisation and shortening of outer and inner segments, while there were seemingly normal photoreceptors in the central retina. With progression of disease there was an increased loss of visual cell nuclei, and outer and inner segments were degenerating or lacking in most parts of the retina. The end stage showed a generalised loss of photoreceptors with the external limiting membrane in close contact with the pigment epithelium. Abnormalities were not found in the pigment epithelium, as seen by light microscopy, at any stage of the disease process. Electron microscopy (to be published) of early cases confirmed that rods were affected earlier than cones but that there was an involvement of both rods and cones at later stages.

A fairly good correlation was found between the stage of disease, as seen by ophthalmoscopy, and functional integrity of the retina, shown by the intensity-amplitude relationship for the dark adapted ERG. The stages of the disease corresponded more to the rod system than to the cones, which was found by comparing scotopic b-wave and cone flicker responses.

The time course of the ERG did not show any major abnormalities. Dim light stimuli during scotopic conditions and 30 Hz flicker stimuli showed a normal implicit time for rods and cones, respectively, in affected animals. A significant delay in b-wave implicit time was found at one of the high light intensities only. Previous studies have shown a delay in rod and cone b-wave implicit time in conjunction with generalised photoreceptor disorders.[10 11] More recently, however, normal rod and cone implicit times were found in miniature poodles affected by a generalised retinal degenerative disease.[12]

The retinal degeneration found in this strain of Abyssinian cats shows many similarities to classical retinitis pigmentosa in man. In the latter disease, first the midperipheral and then the peripheral retina is most frequently affected prior to that of the posterior pole, with a progressive loss of night vision. Rods are more severely affected than cones.[13] Low-voltage ERGs or non-recordable ERGs are frequently found in RP patients, though in early cases ERGs with only slight alterations have been seen occasionally.[14 15] It is conceivable that this strain of Abyssinian cats may be a new and important animal model for the study of this devastating retinal disease in man.

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Bilateral nanophthalmos, pigmentary retinal dystrophy, and angle closure glaucoma—a new syndrome?

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SUMMARY An unusual case of bilateral nanophthalmos with pigmentary retinal dystrophy and angle closure glaucoma is presented. This is probably the first published report of the established association of all these three entities in the same patient. The aetiological possibilities and clinical significance are discussed.

The not infrequent association of angle closure glaucoma with primary pigmentary degeneration of the retina has been known since 1862.[1] The susceptibility of microphthalmic eyes to develop angle closure glaucoma is well established.[2] A few reports are also available of microphthalmos with pigmentary retinal dystrophy.[3] Interestingly enough, the manifestation of all these three disorders in the same patient does not seem to have been conclusively documented previously.

Case report

A 56-year-old male teacher presented complaining of poor vision, more so in the right than the left eye, since childhood. He had used high hypermetropic glasses since the age of 12 years, when he had a corrected vision of 6/12 in both eyes. He also complained of night blindness associated with progressively worsening vision since the age of 30. Over the last 10 years the vision had further deteriorated in his right eye to finger counting only. Transient blurring of vision on near work had been present for the past six months, without any associated pain or watering.

He was given elsewhere a course of subconjunctival injections in both eyes, but without improvement. However, the vision in the left eye remained useful. No history of pain, redness, watering, or coloured haloes could be elicited. His personal and family histories were non-contributory.

General examination revealed a tall, averagely built male, with no systemic abnormality. On ocular examination, his best corrected visual acuity was counting fingers at 2 metres OD and 6/24 OS with +14 Dsph OU. The eyeballs were deep set (Fig. 1) with narrowed palpebral apertures, small corneas (horizontal diameter of 9·5 mm both eyes), markedly shallow anterior chambers, and minimal lenticular changes. The pupils showed an anisocoria; the right pupil was the larger (Figs. 2a, b) and gave a poor

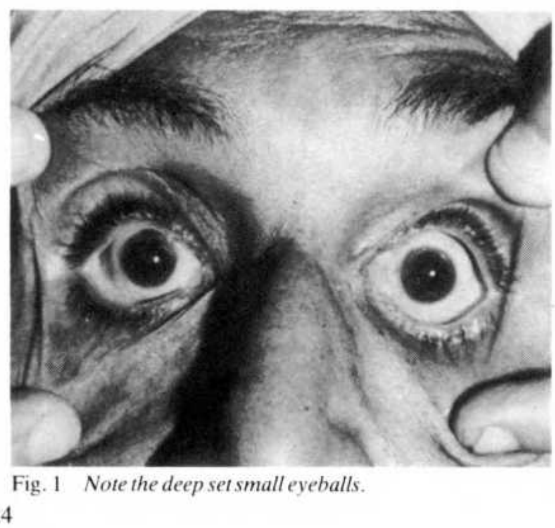

Fig. 1 *Note the deep set small eyeballs.*

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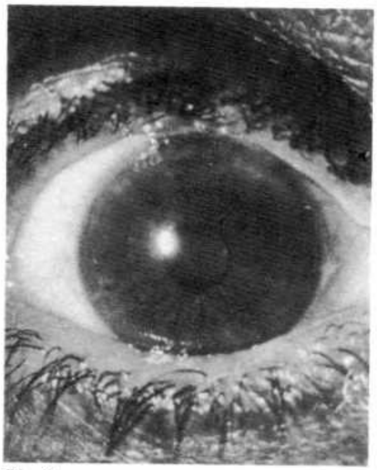
Fig. 2a

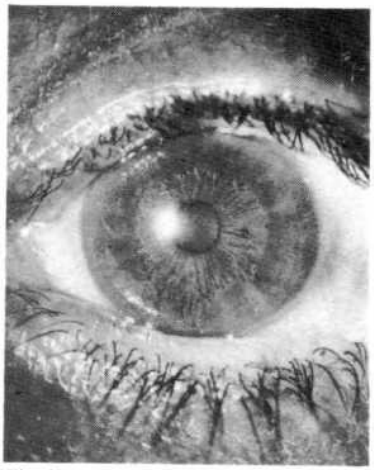
Fig. 2b

Fig. 2 *Close-ups of the* (a) *right eye and* (b) *left eye. Note the larger pupil in the right eye, with a normal iris pattern.*

direct response to light. The consensual light reflex in the left eye was also sluggish. No patch of iris atrophy was noted in either eye.

Ophthalmoscopic examination through slightly hazy media revealed hypermetropic discs with mild pallor (more marked in the right eye), normal cup-disc ratios, attenuated arteries, and bone spicule pigmentation together with clumps of pigment, especially in the perivascular area in the equatorial region (Fig. 3). The macula also showed pigmentation, more in the right than the left eye.

On biomicroscopy only a chink of the anterior chamber about ¼ the thickness of the cornea was found adjacent to the limbus in both the eyes (Figs. 4a, b, 5a, b).

On investigation the intraocular pressures (IOP) were normal. A narrow angle with markedly narrow entry was observed gonioscopically in both eyes. Dry refraction failed to improve the vision any further. On Goldmann perimetry, a bilateral constriction of both central and peripheral fields, with a ring scotoma in the 20–30° isoptres, was recorded.

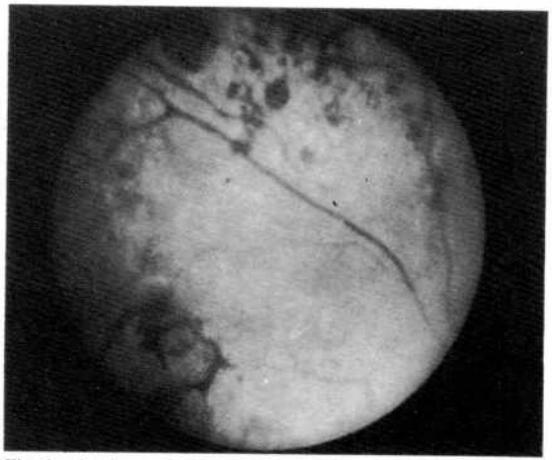
Fig. 3 *Right eye fundus photograph (through slightly hazy media) showing a pale disc, attenuated arteries, and pigmentary dystrophy. Note the macular involvement.*

Anterior chamber depths of 1·90 mm OD and 1·94 mm OS were measured by the Haag-Streit 900 pachometer. On A-scan biometry the axial lengths were 18·2 mm OD and 18·3 mm OS, with a lens thickness of 4·9 mm OU, and anterior chamber depths of 1·90 mm OD and 1·92 mm OS.

Electroretinography recordings (without pupillary dilatation) were subnormal in both eyes. Visually evoked responses using the pattern reversal stimuli showed no detectable pattern in the right eye and an amplitude of 8 μV with a latency of 105 ms in the left eye (control amplitude 6–10 μV; latency <100 ms).

The visual prognosis was explained to the patient. In view of his shallow anterior chambers and high hypermetropic status he was not advised to have provocative tests or miotics, but only a periodic follow-up with us, for which he regularly attended for four months.

Six months later he presented with complaints of nausea, blurred vision, coloured haloes, redness, and pain and watering of four days duration in the right eye. Owing to unavoidable circumstances he could not attend the hospital immediately on the onset of these symptoms, though he had been told of the possibility of their occurrence and their significance.

Ocular examination carried out then revealed a best corrected visual acuity of finger counting at 1 metre OD and 6/24 OS. Other salient features in the right eye included marked conjunctival and ciliary congestion, corneal oedema, a few keratic precipitates with an aqueous flare, a somewhat oval, fixed,

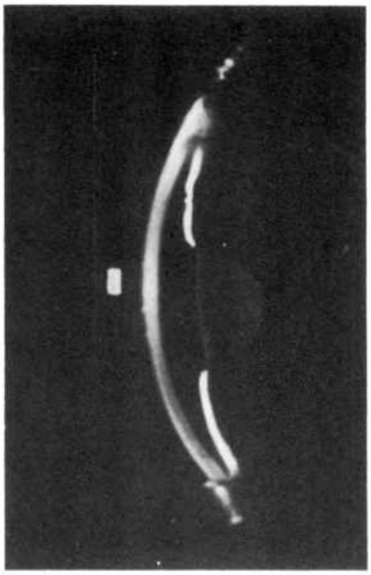

Fig. 4a

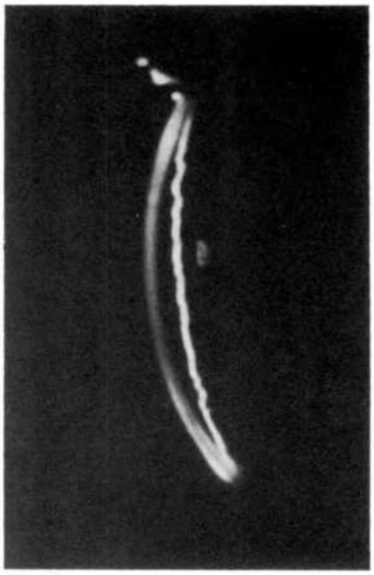

Fig. 4b

Fig. 4 *Initial slit-lamp photographs of the right eye. Note the* (a) *markedly reduced depth of the anterior chamber adjacent to the limbus, more evident in* (b) *a peripheral section.*

mid-dilated pupil with sphincteric atrophy (Figs. 6a, b), and a raised IOP of 54 mmHg in the right eye. On gonioscopy a closed angle with peripheral anterior synechiae in the right eye and a narrow angle with narrow entry as before in the left eye were observed. A diagnosis of an acute attack of angle closure glaucoma in the right eye was made and medical therapy promptly instituted. The control of IOP in the right eye being inadequate on miotics alone, a trabeculectomy was performed, resulting in satisfactory control of the IOP postoperatively. He is awaiting a prophylactic peripheral iridectomy in the left eye.

Discussion

The term nanophthalmos (pure microphthalmos) indicates an eye which is normal other than being

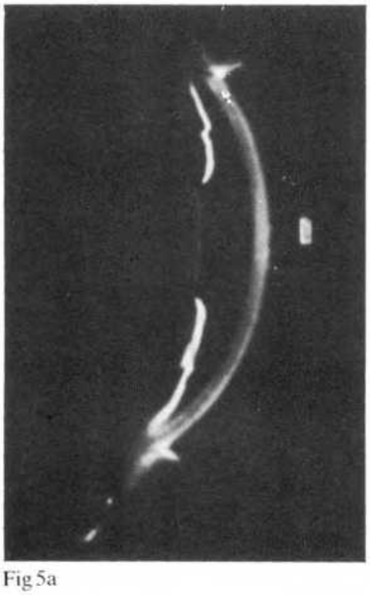

Fig 5a

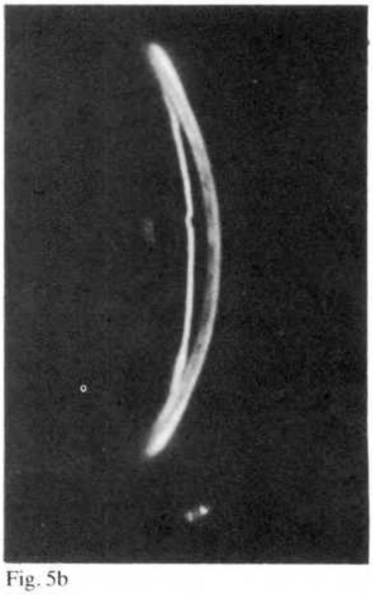

Fig. 5b

Fig. 5 (a, b) *Slit-lamp photographs of the left eye showing features similar to those of the right eye (as seen in Fig. 4).*

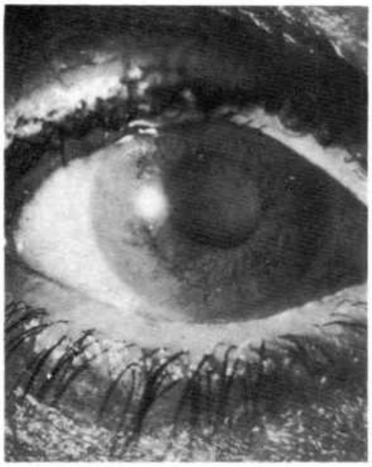

Fig. 6a

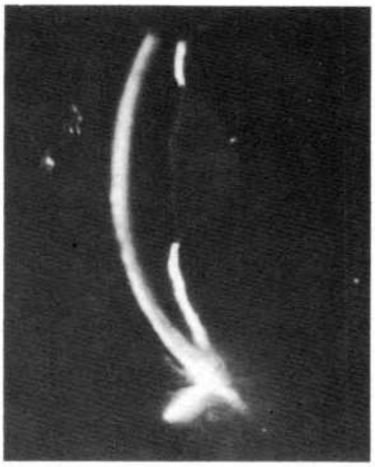

Fig. 6b

Fig. 6 (a) *Close-up of the right eye during acute attack of angle closure glaucoma: the hazy cornea and oval mid-dilated pupil with sphincteric atrophy are obvious.* (b) *The corneal oedema is more evident in the slit-lamp section: the peripheral chink of anterior chamber is no longer visible (compare with Fig. 4a).*

uniformly reduced in size.[2,4,5] Measurements of the nanophthalmic eye have been infrequently documented. The critical value of the eyeball dimensions at which an eye is judged nanophthalmic have not been clearly defined. Two-thirds of the normal volume and an axial length of 16–18·5 mm have been proposed.[4] A reduction of the normal eye size by 15% has also been suggested as a sufficient criterion for diagnosing nanophthalmos.[5] By these criteria our patient has bilateral nanophthalmos. However, a nanophthalmic eye has also been categorised as one having a sagittal diameter of 13–17 mm.[6] Besides congenital angle anomalies, which are common[4] and predispose nanophthalmic eyes to simple glaucoma later, these eyes are usually hypermetropic, with a relatively large lens and a remarkably high ratio of lens volume to eye volume.[7] This plays an important contributory role in the shallow anterior chamber encountered in nanophthalmos. Presumably growth of the lens with age increasingly crowds the already developmentally shallow anterior chamber, thereby rendering these eyes susceptible to angle closure glaucoma, as in our case.

Our findings on investigation of the patient corroborated the clinical diagnosis of pigmentary retinal dystrophy. The clumps of pigment along with the classical bone spicule pigmentation, together with the macular involvement, are recognised variant features. Primary pigmentary degeneration of the retina is well known in having certain systemic and ocular associations, of which glaucoma is well documented. Most authors mention open angle glaucoma.[8] The association of angle closure glaucoma with retinitis pigmentosa seems to be rather rare in published reports, and it has even been proposed that this association may be fortuitous.[9] Whatever the type of glaucoma, the clinical and histopathological reports available have not elucidated its pathogenesis in relation to retinitis pigmentosa.[1,9]

Maldevelopment of the retina, retinitis pigmentosa, and other retinal anomalies have also been reported in nanophthalmos.[3,4] The aetiology of the association of nanophthalmos and retinitis pigmentosa also remains unexplained. It is possible that in the basically underdeveloped eye of nanophthalmos the lack of full development of the retina in the later part of fetal life is responsible for pigmentary retinal dystrophic changes.

The association of nanophthalmos with pigmentary retinal dystrophy,[3] pigmentary retinal dystrophy with glaucoma,[1,8,9] and glaucoma with nanophthalmos[2,4–7] has been reported previously. However, the simultaneous occurrence of all these three entities, namely, nanophthalmos, pigmentary retinal dystrophy, and glaucoma, seems to have been described only twice.[10,11] The first report,[10] in three brothers, was apparently of simple glaucoma, there being no mention of detailed symptomatology or of angle closure glaucoma. In the second report four patients of the 13 affected seem to have had ocular features suggestive of angle closure glaucoma, though no measurements of anterior chamber depth or gonioscopic or biometric data were included.[11] Again, in this rather detailed communication there is no categorical mention of the term angle closure glaucoma. This report has subsequently been interpreted as 'microphthalmia' with a 'somewhat atypical dystrophia retinae pigmentosa' and 'ocular hypertension with subacute attacks'.[3]

In our patient there is no doubt of the established diagnosis of angle closure glaucoma in association with nanophthalmos and pigmentary retinal dystrophy. In the absence of other family members being affected this case seems to have been sporadic in nature.

Since nanophthalmic eyes seem to be anatomically predisposed to angle closure glaucoma, and pigmentary retinal dystrophy has been reported with both these entities, it is possible that the occurrence of all three in a given eye may have been overlooked in earlier reports. It appears that if a case presents with any two of these three entities, it is worth diligently searching for the third component, even if only to exclude it.

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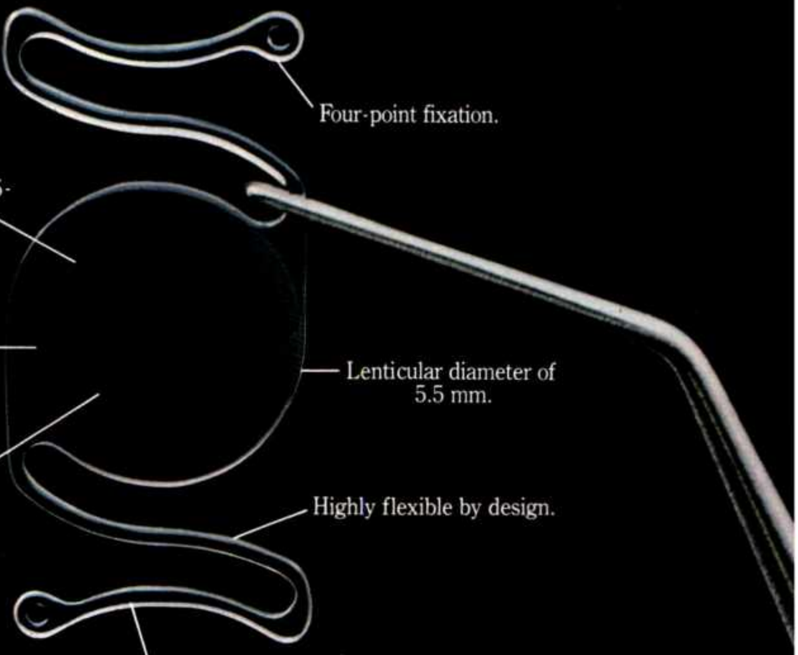

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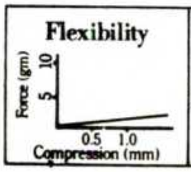

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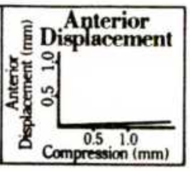

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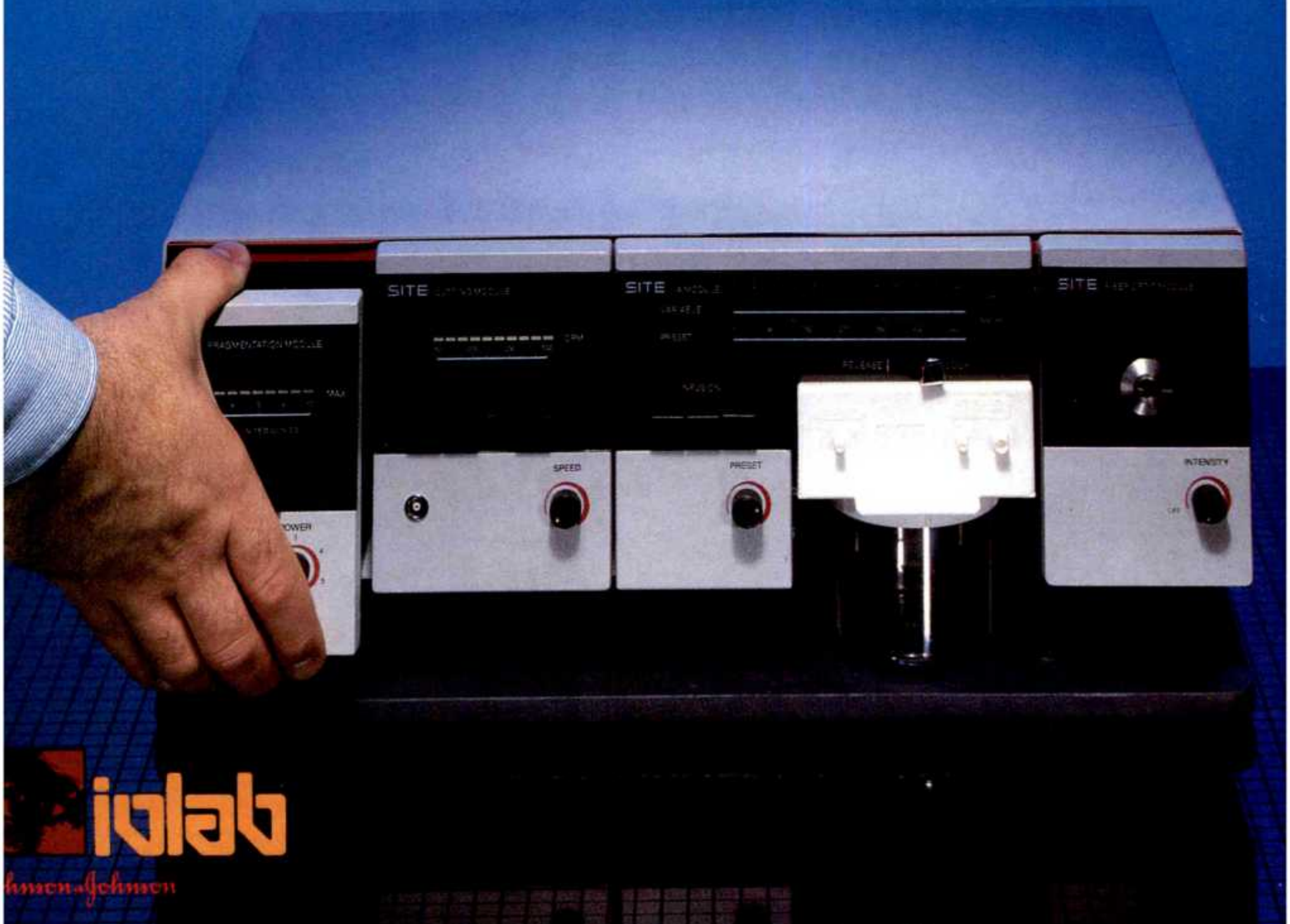

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Conjunctival sign in sickle cell anaemia: an in-vivo correlate of the extent of red cell heterogeneity

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SUMMARY A consecutive series of 22 stable adult inpatients with sickle cell anaemia were examined for the presence and severity of spontaneous 'comma' signs of the conjunctiva. Fifteen patients had severe conjunctival signs (more than 10 commas in the worse eye). The presence of severe conjunctival signs was associated with a broader distribution of intraerythrocytic haemoglobin concentrations ($p=0\cdot0005$). The patient group with severe conjunctival signs was not found to be significantly different from the group without such signs for age, sex, haemoglobin value, reticulocyte count, α-globin gene number, percentage fetal haemoglobin, or the proportion of very dense cells (CHC >37 g/dl). Thus the singular heterogeneity of the erythrocytes in sickle cell disease may be indicative of the factor(s) responsible for the diagnostic comma sign.

The conjunctival sign in the sickle haemoglobinopathies has been termed the 'comma' sign because of its clinical appearance as short, truncated, isolated, dark vascular segments, and it is considered pathognomonic for these disorders.[1-3] It is of particular interest to clinicians not only because it can be readily detected and quantitated, but because its pathophysiology may reflect functionally and morphologically more deleterious microvascular events in other jeopardised tissues. The severity of the sign has been reported to be correlated with the number of irreversibly sickled cells (ISCs).[4] However, the subjective quantification of the ISCs entails the limitation of interobserver variability. Recently, several cellular and molecular factors that may affect the severity of sickle cell disease have been identified.[5] In particular, it is now possible to measure the distribution of intracellular haemoglobin concentrations,[6,7] which appears to be the major factor that determines intracellular sickle haemoglobin polymerisation in peripheral blood. The purpose of the present investigation was to explore the relationship between the conjunctival comma sign and several suspected modifying factors in patients with stable sickle cell anaemia.

Patients and methods

We studied a consecutive series of 22 patients with stable homozygous sickle cell disease who were admitted to the Cinical Hematology Branch of the National Institutes of Health for routine follow-up from April 1983 to April 1984. The patients were not in crisis during one month before or after the study date, had not received a blood transfusion in the prior four months, and were not receiving long-term medication other than folic acid. Their ages ranged from 19 to 51 years.

The diagnosis of sickle cell anaemia was made on the basis of haemoglobin electrophoresis on alkaline cellulose acetate and on acid citrate agar, DNA analysis of bone marrow aspirates, and peripheral blood examination; when possible it was confirmed by family studies.

Assessment of the conjunctival signs was performed by one of us (MSR) with the slit lamp biomicroscope. Each quadrant was examined in turn. The largest number of commas in any quadrant of either eye was the rating for that patient. The

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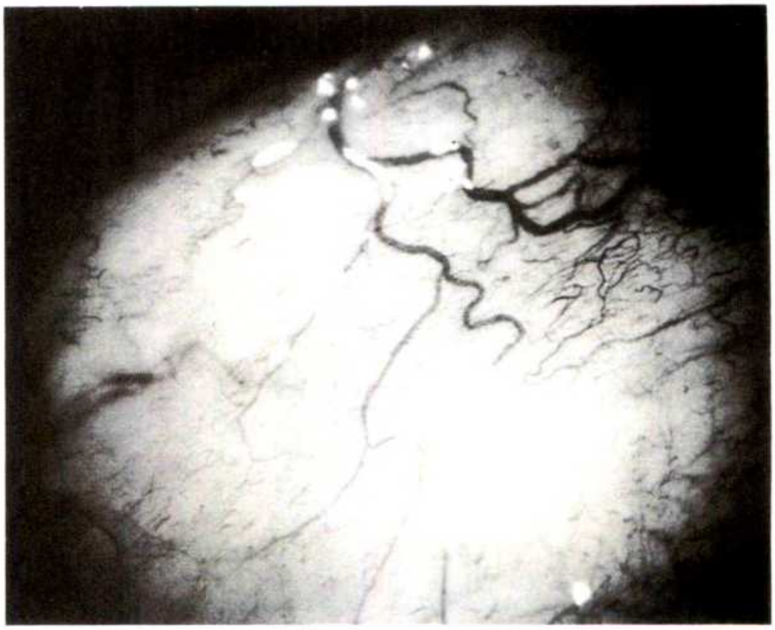

Fig. 1 *Severe comma sign in sickle cell anaemia.*

occurrence of 10 or fewer commas was graded as minimal, more than 10 commas as severe (Fig 1).

The haematological examination, performed by one of us (GPR) on the day of the conjunctival examination, included the total haemoglobin value, the reticulocyte count, the fraction of haemoglobin F (measured spectrophotometrically after alkaline denaturation), and the mean corpuscular haemoglobin concentration (MCHC), which was derived manually from the total haemoglobin and the packed cell volume. For each patient the number of α-globin genes was determined by restriction endonuclease analysis of DNA obtained from peripheral white blood cells by means of the α-globin specific plasmid JW-101.[8,9] The red cell density profile for each patient was determined by the calibrated phthalate ester density method.[7]

Conjunctival and haematological assessments were done in a masked fashion and were repeated on a number of subjects, which confirmed the stability of these measurements. Statistical methods included the t test for variables with Gaussian distributions, the rank sum test for variables with non-Gaussian distributions, and χ^2 tests for categorical variables.[10] Because several comparisons were tested, an association was considered significant if the calculated p value was less than 0·01.

Results

Among the 22 patients with sickle cell anaemia 7 had minimal and 15 had severe conjunctival signs (Table 1). Although there were no significant differences between these two groups with respect to age, sex, haemoglobin value, MCHC, reticulocyte count, or the percentage of fetal haemoglobin, there was a suggestion that the presence of severe conjunctival signs was associated with evidence of an increased

Table 1 *Haematological indices and comma sign in sickle cell anaemia*

	Comma sign		*Significance level (2-tail p-value)*
	Minimal (n=7)	*Severe (n=15)*	
Age (years)*	32·3 (9·5)	30·9 (7·3)	0·75
Sex (% women)	42·9	26·7	0·79
Hb (g/dl)†	9·15 (0·32)	8·69 (1·08)	0·07
MCHC (g/dl)*	33·08 (1·83)	34·74 (2·07)	0·08
Reticulocyte (%)*	8·2 (2·8)	11·6 (5·6)	0·07
HbF (%)†	2·0 (3·0)	1·4 (0·6)	0·40
Dense Cells (%)†	4·66 (4·18)	8·00 (8·34)	0·31
D_{50} (SG units)*	1·100 (0·006)	1·102 (0·004)	0·41
R60 (SG units) $\times 10^{-3}$*	10·04 (2·96)	17·80 (5·80)	0·0005

Hb=haemoglobin. MCHC=mean corpuscular haemoglobin concentration. HbF=fetal haemoglobin. Dense cells=erythrocytes with specific gravity >1·120 or corpuscular haemoglobin concentration >37 g/dl. D_{50}=median red cell density. R60=specific gravity units, range over which the middle 60% of red cell densities are distributed (see Rodgers *et al*[7]).

*Mean (standard deviation).

†Median (interquartile range/2). Note: the interquartile range contains half the total frequency.

haemolytic rate (i.e., a lower haemoglobin value, p=0·07, and a higher reticulocyte count, p=0·07). Our group included two patients with sickle cell disease (SS) and coexisting homozygous α-thalassaemia (α-/α-) and five patients with SS and heterozygous α-thalassaemia (α-/αα), which did not significantly alter the expression of the conjunctival sign (p=0·13 for trend analysis). The red cell density profiles were not significantly different between the groups for the fraction of very dense red cells (>1·120 specific gravity or corpuscular haemoglobin concentration (CHC) >37 g/dl) or for the median density value (D_{50}) of red cells. On the other hand the density range over which the middle 60% of red cell densities (or intracellular haemoglobin concentration) were distributed (R60 value) was markedly greater in the group with severe conjunctival signs (p=0·0005). A multiple logistic analysis showed that, once the R60 value was accounted for, the two groups did not differ for any other variable.

Discussion

The comma sign in SS, although easy to assess clinically, is labile and subject to known variations.[1,2] In this study all the patients had stable sickle cell anaemia and had not been recently transfused, and prolonged exposure of the conjunctiva to the heat of the slit lamp was avoided during the examinations.

Although this microvascular abnormality is pathognomonic of sickle cell disease, its pathogenesis remains obscure. Equally uncertain is why this ocular manifestation is less pronounced in genetic variants of SS. Previous investigators have found a significant correlation between the severity of the sign and the number of ISCs.[4] Some have interpreted these phenomena as due to in-situ sickling; other groups have pointed out possible contributions of vasomotor tone and sludging of flow[11,12] to the comma sign. Though ISC counts were not assessed systematically, data available for nine (35%) of our patients confirmed the previously reported association. The four patients in the minimally affected group had a mean ISC count of 5·90 (standard deviation 2·41), and the five patients in the severely affected group had a mean ISC count of 17·84 (standard deviation 8·91) (p<0·05 by the *t* test and rank sum test data not shown). This is consistent with the highly significant relationship found in supplementary experiments on 10 SS patients between the ISC count and the degree of red cell heterogeneity, as reflected in the R60 value (p<0·001).[13]

The lack of an association of high levels of haemoglobin F or α-thalassaemia with the severity of the comma sign, which are both thought to reduce the general severity of sickle cell disease,[5] may be due to the relatively small sample size.

Microvascular flow in patients with sickle cell disease is constantly jeopardised by virtue of intracellular polymerisation of deoxyhemoglobin S,[14] mostly by the cells containing the highest intracellular concentration of haemoglobin S (exclusive of red cell sickling).[15] However, studies of the relationship between the mean corpuscular haemoglobin concentration (MCHC) and indices of disease severity ignore the fact that red cells in patients with sickle cell disease are not homogeneous, but rather comprise several subpopulations with respect to intracellular haemoglobin content.[16] Thus it is not surprising that, although the MCHC was generally higher in severely affected patients, this association was not statistically significant (p=0·08).

In this study the patients with severe conjunctival signs has a much broader range of intracellular haemoglobin concentrations (R60 values) and showed a suggestion of a greater degree of haemolysis as reflected by lower haemoglobin values and higher reticulocytes counts. Both the conjunctival sign and conjunctival blood flow in sickle cell patients are affected by local heat, vasoactive substances, sickle cell crisis, and blood transfusions.[11,12] We speculate that these conjunctival microvascular abnormalities may arise from inappropriate or excessive vasoconstriction owing to the local noxious effects of transient ischaemia mediated by rheologically compromised erythrocytes. The proportional decline in the severity of the conjunctival sign in patients with genetic variants of SS (i.e., SC, S-ß$^{+}$-thal, S-HPFH, etc.),[2,12] in which the intracellular polymerisation of haemoglobin S is inhibited,[17] with the production of a more homogeneous cell population[18] would also support this hypothesis.

Obviously the factors governing red cell heterogeneity in sickle cell disease and their relative impact on the microvasculature will require further exploration. However, this study does show that the severity of the conjunctival sign is strongly correlated with the heterogeneous distribution of intraerythrocytic haemoglobin concentrations. Further studies are in progress to determine whether this sign can be used to monitor therapy targeted at favourably modifying intracellular haemoglobin S levels.

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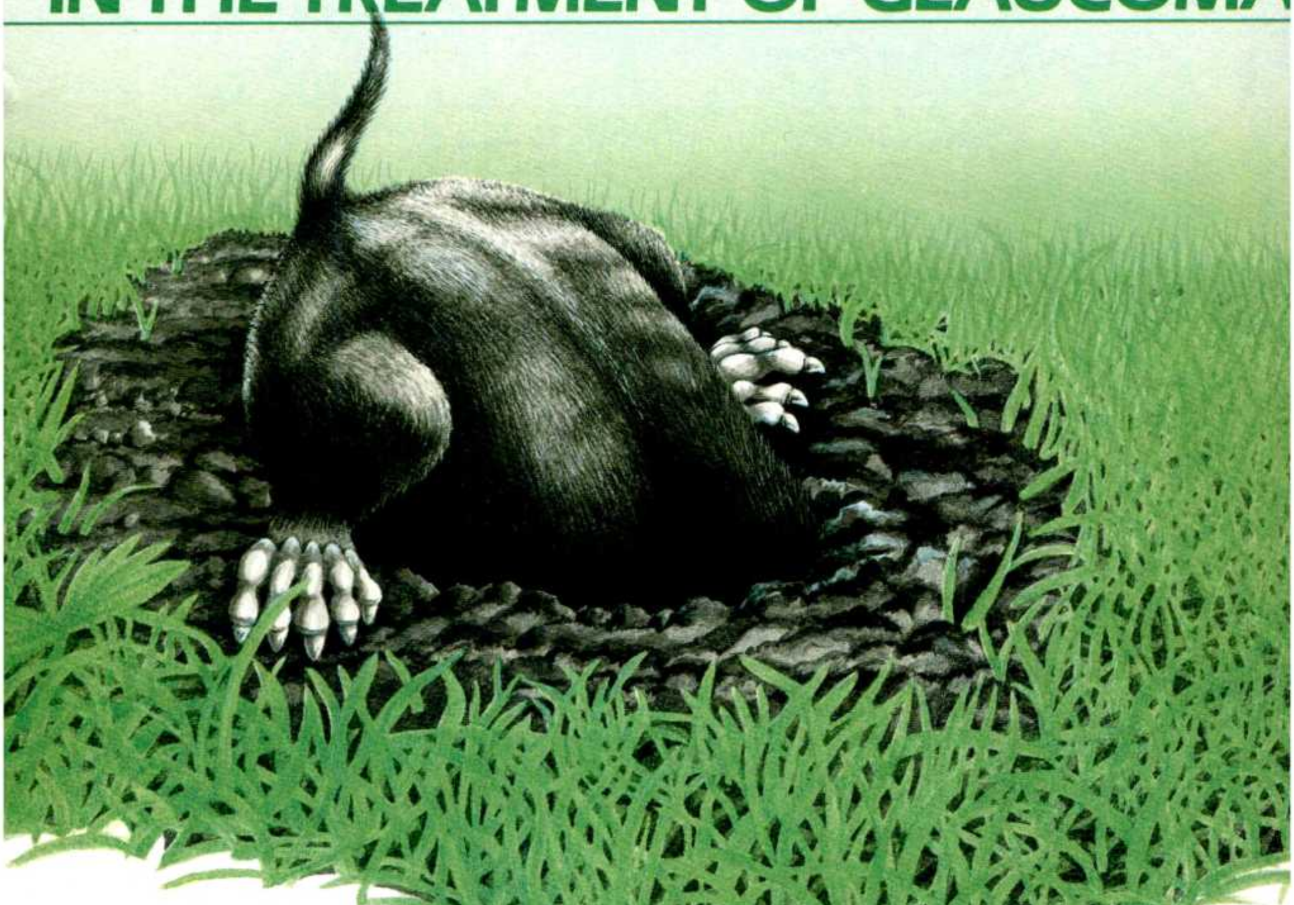

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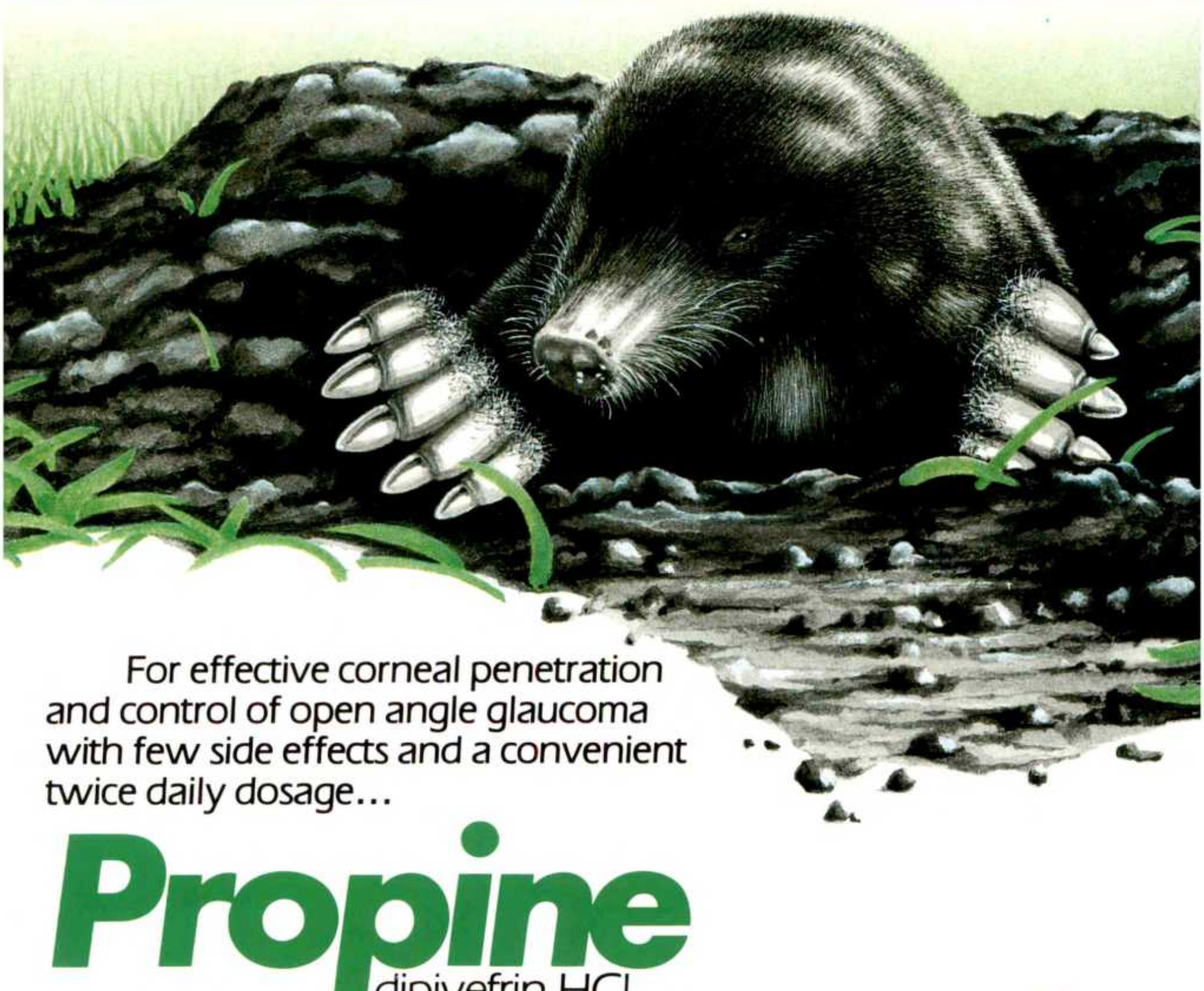

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Chronic ocular ischaemia

SIR, I was very much interested to read the paper by Sturrock and Mueller on 'Chronic ocular ischaemia'.[1] The authors,[1] commenting on the fundus changes seen in *one of their seven cases*, stated. 'The chance finding of blot haemorrhages distributed in the midperiphery of the retina in case 2 associated with a congested appearance of the veins which showed sludging probably indicates ischaemia of more gradual onset. This appearance, which has been misleadingly called venous stasis retinopathy,[2] must be distinguished from that due to central retinal vein thrombosis.[3] Regrettably this same term, venous stasis retinopathy, was subsequently applied to certain cases of central retinal vein thrombosis,[4] thereby compounding the confusion.'

These comments, unfortunately, raise an extremely important controversy which requires clarification. I would preface my comments by pointing out that over the past 10 years we have been prospectively conducting long-term studies on various types of ocular vascular disorders, and have collected data so far on about 450 patients with central retinal vein occlusion (CRVO) and about 200 patients with carotid artery disease (CAD). Based on our experimental and prospective clinical studies on CRVO I divided CRVO into ischaemic and non-ischaemic varieties.[4-7] The non-ischaemic CRVO represents simply a stasis of retinal venous circulation and I designated it 'venous stasis retinopathy' (VSR). When I used the term 'VSR' I was fully aware that Kearns and Hollenhorst[2] had used the same term for what they felt was a specific type of retinopathy associated only with severe CAD. Kearns and Hollenhorst[2] postulated that 'VSR' was due to retinal hypoxia, secondary to CAD Our detailed studies have indicated that the vast majority of the 'VSR' cases described by Kearns and Hollenhorst[2] and others were in fact cases of mild non-ischaemic CRVO; this was the basis of my using the term 'VSR' to describe non-ischaemic CRVO. I discussed this subject recently at length elsewhere [4,7] Kearns,[3] to rebut my views on the subject, recently discussed in detail the differential diagnosis between these two types of retinopathy and claimed that his 'VSR' is very different from 'CRVO.' He stated, for example, that fluctuating blurred vision, a specific pattern of distribution of retinal haemorrhages, absence of optic disc oedema, and ocular hypotony are typical of 'VSR' due to CAD. Our detailed prospective long-term studies on about 350 cases with non-ischaemic CRVO, clearly revealed that these features *are seen* in non-ischaemic CRVO, with fluctuating blurred vision and ocular hypotony being very common findings.[6,8]

In contrast to our studies on CRVO there is no systematic study on the natural history or other aspects of 'VSR' attributed to CAD[2]; all the reports making that claim are anecdotal, mostly based on a single examination or extremely short follow-up. Experimental carotid artery occlusion also failed to produce retinal changes typically seen in 'VSR' [9,10] Generalised severe atherosclerosis in carotid arteries produces CAD, in the coronary arteries it produces myocardial infarction, and in the central retinal artery it contributes to secondary CRVO.[4] Since most patients with CAD suffer from myocardial infarction,[4] this in no way means that CAD and myocardial infarction are cause and effect; the same logic applies to CAD and VSR (mild non-ischaemic CRVO). Evidently all three conditions are simply independent manifestations of severe generalised atherosclerosis. Thus it can be concluded that CAD and VSR are *not* cause and effect but are two independent manifestations of severe generalised atherosclerosis

While I question the validity of the concept and use of the term 'VSR' for the retinal changes being erroneously attributed to CAD, I have seen, in some patients with the latter disease, low retinal artery pressure, irregular calibre, and stasis of circulation in the major retinal vessels, and occasionally neovascularisation on the optic disc; however, *this fundus picture is very different from that seen in VSR.* I fully agree with Kearns[3] that a more appropriate term is 'chronic ischaemic retinopathy' for the retinal changes secondary to severe CAD, and that their[2] original term 'VSR' to describe the retinopathy 'was unfortunate' and misleading. Unfortunately, most of the cases reported as 'chronic ischaemic retinopathy' by Kearns and his colleagues and other authors are in fact mild non-ischaemic CRVO, and only a very small proportion of their cases represent true 'chronic ischaemic retinopathy ' Thus they have lumped non-ischaemic CRVO and 'chronic ischaemic retinopathy' under the title of 'VSR'—the two are very different types of retinopathy Hence the present confusion.

The field of medicine is littered with myths, originally drawn from simple clinical impressions, anecdotal reports, personal biases, defective experiments, erroneous interpretations, and temporary lapses of famous physicians. These myths come to be regarded as 'established facts.' Any attempt to weed out myths is met with severe resistance and even ridicule. The original concept of VSR, put forward by Kearns and Hollenhorst[2] on simple clinical impression and little scientific evidence, falls into such a category When I first advocated the use of the term 'VSR' for non-ischaemic CRVO, I had no intention of creating 'confusion'; on the contrary I wanted to eradicate the erroneous concept and give a strictly descriptive term for non-ischaemic CRVO I still feel the term 'VSR' best reflects the clinicopathological features of non-ischaemic CRVO.

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Sɪʀ, Professor Hayreh attempts to circumvent the confusion resulting from the use of the term venous stasis retinopathy to describe two different retinal vascular disorders by claiming that most published cases of 'VSR' are actually VSR —i.e., that Kearns, Hollenhorst, and others misdiagnosed cases of central retinal vein occlusion as being ischaemic in origin due to carotid artery disease. Paradoxically, Professor Hayreh is prepared to challenge, wholesale, diagnoses made by experienced ophthalmologists without, I presume, being able to examine personally the patients in question, yet he decries 'personal biases' and 'erroneous interpretations' with which 'the field of medicine is littered.'

Professor Hayreh implies that he was the first to distinguish between the ischaemic and non-ischaemic varieties of central retinal vein occlusion. However, his classification is based on an unsubstantiated belief that the ischaemic-type central retinal vein occlusion is precipitated by blockage of the central retinal artery with arterial circulation becoming re-established 'within a few hours or days.'[1 2] It was Laatikainen and Kohner[3] who pointed out that in some patients central retinal vein occlusion causes extensive retinal capillary closure associated with a high risk of developing thrombotic glaucoma. It is this consecutive retinal ischaemia, also seen after retinal branch vein occlusion, to which the term ischaemic-type central retinal vein occlusion refers and not a hypothetical, transient interruption of the arterial blood supply to the retina.

Use of the words 'stasis' and 'haemorrhagic' to distinguish the two main forms of central retinal vein occlusion, both of which are characterised by slow perfusion and varying degrees of haemorrhage, is illogical. More importantly, the use of the two categories venous stasis retinopathy and haemorrhagic retinopathy may mislead the unwary into thinking that central retinal vein occlusions can be neatly subdivided into two types, whereas of course the retinal capillary response following central vein occlusion covers a spectrum with many patients showing well preserved capillary perfusion, some showing patchy non-perfusion and a minority developing very extensive capillary closure[4] Some patients with initially good capillary perfusion or only small areas of non-perfusion following central retinal vein occlusion may later develop progressively larger areas of retinal ischaemia, leading to an increased risk of rubeosis. In such cases it is easier to think of progressive retinal ischaemia rather than having to change the diagnosis from venous stasis retinopathy to haemorrhagic retinopathy.

In conclusion, the terms venous stasis retinopathy and haemorrhagic retinopathy should be abandoned.

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Safety glasses only for boys?

Sɪʀ, Belated congratulations to V Tommila and A Tarkkanen on their paper on incidence of loss of vision in the healthy eye in amblyopia[1] Their findings are most important and significant. I would like to know what the sex incidence was for the 23 patients in their group as a whole and especially the sex incidence for those 12 patients who lost their eye as a result of trauma.

From Vereecken and Brabant's work[2] one may suspect that trauma is almost always in males If so, one would not have to insist that the girls with permanent amblyopia wear safety glasses—only the boys That is, the probability of a permanently amblyopic female losing her good eye due to an accident might drop to perhaps 1:10000, while the probability for a boy would approach 1:300 (i.e., 1·75/500).

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2 Vereecken EP, Brabant P Prognosis for vision in amblyopia after the loss of the good eye *Arch Ophthalmol* 1984, **102**: 220–4.

Sɪʀ, We are grateful indeed for the letter of Dr Romano. As a reply to his question about the sex incidence of our series we can state that there were 17 males and six females. Of the females two were children aged 9 and 12 years. We agree with Dr Romano about the importance of suggesting safety glasses for patients with permanent amblyopia.

Although the probability of a permanently amblyopic female losing her good eye is low, we insist that the girls should also wear safety glasses because their good eye may be a target of flying objects, such as stones thrown by the boys.

Helsinki University Eye Hospital, AHTI TARKKANEN
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Finland

K-Y jelly as a gonioscopy fluid

Sir, Mr H K Mehta reported 'A new use of K-Y jelly as a gonioscopy fluid'.[1] Apparently he was unaware that Aquino and Francisco had described the successful use of K-Y jelly in gonioscopy 14 years previously.[2]

Aquino and Francisco found that clear images were obtained when the transparent K-Y jelly was used with Goldmann three-mirror and Hruby contact lenses. Its high viscosity made the application of the gonioscopy lens to the eye easy and minimised bubble formation during the examination. The authors compared the effects of K-Y jelly in one eye with those of hydroxypropylmethylcellulose 0·5% solution in the other eye of 50 patients. K-Y jelly caused less decrease in visual acuity and fewer complaints (blurred vision, haloes, lacrimation, periorbital or orbital pain, and foreign body sensation). The preparation was not toxic to the corneal epithelium as judged by rose bengal staining. The K-Y jelly remained sterile during the duration of their study.

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LEONARD APT

References

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2 Aquino MV, Francisco RM K-J jelly in gonioscopy. *Philippine J Ophthalmol Otolaryngol* 1972; 4: 169–72.

Sir, I am grateful to Dr Leonard Apt for bringing to my notice the previous work by Aquino and Francisco describing the successful use of K-Y jelly in gonioscopy I was completely unaware of this work, and give my unqualified apology to Dr Aquino and Dr Francisco. I am pleased to see that our study has produced the same conclusion arrived at by them. It is a sad reflection on possibly the inertia of the ophthalmic profession that their suggestion made 12 years ago has not been taken up by the profession.

I would like to take this opportunity to state that there has been a tendency to use the jelly in liberal amounts to fill the cup of the gonioscope. With our further experience we now use only enough jelly to fill one quadrant of the gonioscope cup. Even this amount allows successful gonioscopy on the second eye without recharging the gonioscope cup with the jelly.

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HEMANT MEHTA

Eye injuries due to explosion of bottles

Sir, I have read with interest the article on 'Ocular injuries from carbonated soft drink bottle explosions' by Mahmoud Al Salem and S M M Sheriff,[1] where they reported 16 cases of ocular injuries in Kuwait, Arabian Gulf. In their report the bottle cap was responsible for concussion in two cases only In July 1978 we published an article entitled 'Eye injuries due to explosion of carbonated drink bottles'[2] in which 26 injured persons were reported. In 80% the eye was injured by the flying cap of the bottle and in 20% by glass fragments of the exploding bottle; 20% of them have become legally blind and in 15% vision has remained seriously impaired.

To prevent this injury the Israel Institute of Standards imposed stricter regulations for ensuring the safety of bottles containing carbonated soft drinks It insisted on an improved cap and the replacement of glass bottles by non-returnable plastic ones. Since those measures were taken, only rare cases of eye injury by carbonated soft drink bottles in Israel have occurred.

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AVISAR RAHAMIM
SAVIR HANNA

References

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Sir, We were not aware of the article of Drs Avisar and Savir on the subject,[1] though we did our best to review all the available English literature on it. Their article was in Hebrew, though it had a summary in English. In our series[2] two cases (14%) of concussion injury were caused by flying caps as opposed to the majority of perforating injury caused by flying pieces of shattered glass of the bottle. The same type of injury was described by Mondino *et al* [3]

We have discussed with the experts in the management of this industry the difference in the two countries It could be attributed to possible differences in manufacture, where the bottle is of stronger quality relative to the sealing cap. Therefore it gives way first when there is an increase in pressure

Through the collaborative efforts of official and semi-official organisations in Kuwait the public has been made aware of this type of injury Many people are not using glass bottles in their houses and they have been replaced on a large scale by plastic bottles and tins or plastic wrapped glass bottles of non-returnable type. The incidence of this type of injury has started to decline in our present experience. This problem and other similar problems will be discussed in Ocular Trauma Symposium in Kuwait in April 1985.

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Kuwait.

MAHMOUD AL SALEM
S M M SHERIFF

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Book review

A Colour Atlas of Uveitis Diagnosis. By Joseph B Michelson. Pp. 158. £30·00. Wolfe Medical Publications: London. 1984.

Atlases have a time honoured role in ophthalmology as a teaching and diagnostic aid and the addition of colour can make them objects of beauty too. This is, however, one of the worst books I have read for some time. It contains 305 colour photographs in 152 pages 'to demonstrate those uveitis signs that will familiarize the reader with specific common uveitis disease entities so he can diagnose accurately and treat these very complicated ophthalmologic disorders'. The book is in two parts, 'Signs of uveitis' (106 photographs, 52 pages), followed by short sections on 26 different disease entities.

'Signs of uveitis' is a mixture of photographs of conditions which have apparently at one time or another been referred to the author as an inflammatory disorder Among this random collection are surprises such as retinal macroaneurysms, angiomas, hamartomas, Best's disease, angioid streaks, melanomas, and vernal conjunctivitis. Photographs are presented in random anatomical or diagnostic order without any logical or cohesive pattern, examples of toxoplasmosis for instance, appearing on pages 30 and 31, 36 and 37, and 44. The same illustrations can be repeated again in this section (e.g. Sturge-Weber syndrome no. 16 repeated as 51, 52) or later under the separate disease section, which casts doubts on the range of the available clinical experience and material. Many anterior segment photographs have been taken with a fundus camera which does nothing for their quality and can be bizarre when used to photograph conditions such as an aphthous ulcer. Many illustrations are repetitious. I found seven in the first section which basically show only posterior synechiae. Others are incomprehensible, such as no. 96, supposedly a malignant melanoma, and some of the skin photographs are so badly presented that it is difficult to identify which part of the body that they come from (e.g., 128, 152, 153, 207, 250).

The colour reproduction is dreadful. Ocular photography and colour printing demand the highest standards, but we are treated to fundus and anterior segment photographs in varying shades of purple, brick reds through to blues and greens which bear no resemblance to reality. Some of the worst examples (e.g 4, 11, 281) are published 'courtesy of the Wills Eye Hospital Residents Teaching Collection'. Surely they have a better example of a corneal dendrite than number 11? Many photographs are so poorly reproduced that one cannot see the details, even with the eye of faith. I was unable to see 'prominent Koeppe nodules' in no. 30 or even in its reincarnation as number 121. Illustration no. 20 appears as 'band keratopathy' in turquoise, could it have been photographed with a cobalt blue light? But we see it again as 116 where it is greyish blue. The section on Fuchs's heterochromic cyclitis demonstrates many of the book's failings. Illustration 278 adds a new dimension to the meaning of heterochromia, in 279 'abnormal vessels in the chamber angle' are not visible, posterior subcapsular changes certainly cannot be noted in 280, and 281 is a unique photograph from the Wills collection antedating colour photography by some years. Other notable illustrations in the book are 47, 'A dense vitritis,' and 299, 'Typical fungal fluff ball,' which to all intents and purposes are a diffuse redness and greyish white respectively.

Each section has a short introductory text, usually of less than half a page, and there is a short sentence as a caption to each illustration. I found I had to read many sentences two or three times to understand the West Coast dialect, and some left me puzzled: 'Historically, it may be identified with acid-fast stains such as Zeehl-Nielson (sic) or Fite stain and found in lesions of the retina, choroid, ciliary body, iris, cornea, conjunctiva, and orbit' (discussing ocular tuberculous, p. 123). Some statements such as 229, '60-year-old man presents with such dense vitritis, his slit-lamp appearances simulate a cataract,' give the reader a feeling of unease, and in 264 a fluorescein angiograph of a patient with geographic choroiditis, scleral staining at the edge of the lesion, is confused as a sign of disease activity.

At the end of the book three page of publications are listed in alphabetical order which are up to date and excellent in their own right, but regrettably they are not referred to in the text and so are of little practical use to the reader.

DAVID J SPALTON

Notes

Interspecialty and oculoplasty congress

The 13th Annual Midwinter Interspecialty and International Oculoplastic Society Congress will be held at Casa de Campo, Dominican Republic, on 15–22 February 1986 There will be concurrent programmes on facial plastic surgery and ophthalmic surgery. Details from Congress Administrator, c/o Pierre Guibor, MD, 630 Park Avenue, New York, NY 10021, USA

International Congress of Ophthalmology

The 25th International Congress of Ophthalmology will be held in Rome on 4–10 May 1986 The organising committee requests the submission of abstracts of papers, posters, scientific exhibits, and films. Abstracts must be submitted by 31 October 1985. Just before and after this congress there will be four 'related' symposia in countries other than Italy and 20 'satellite' symposia in various Italian cities. Details are given in the programme. Further information from Roma '86, Coordinating Centre, c/o EGA Congressi, Viale Tiziano 19, 00100 Roma, Italy.

Sarcoidosis conference

The fifth European Conference on Sarcoidosis and Other Granulomatous Disorders will be held in Vienna on 27-30 August 1986 Further information from the secretariat of the conference at: PO Box 9, A-1095 Wien, Austria.

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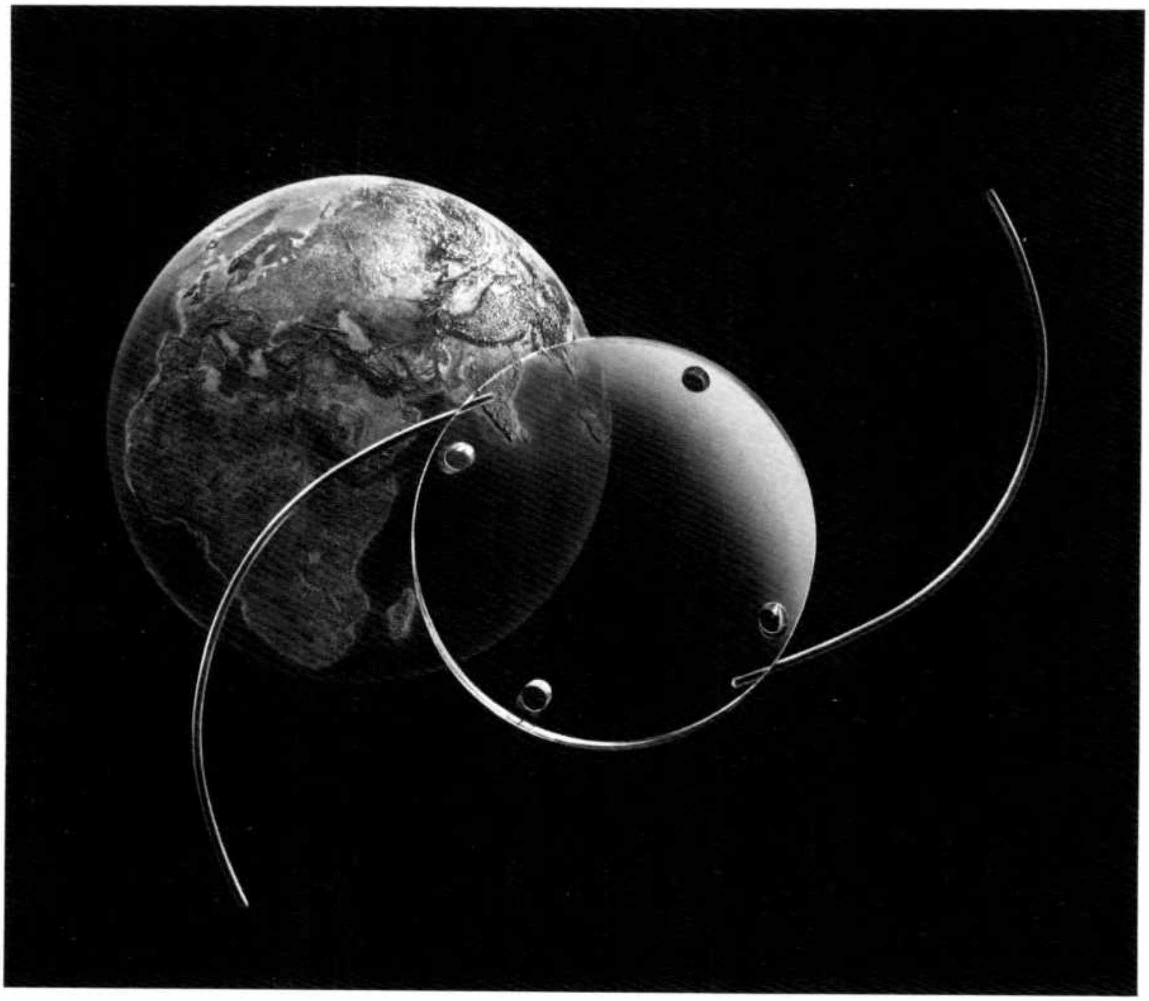

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† Details are obtainable from the British Postgraduate Medical Federation, 33 Millman Street, London WC1N 3EJ.

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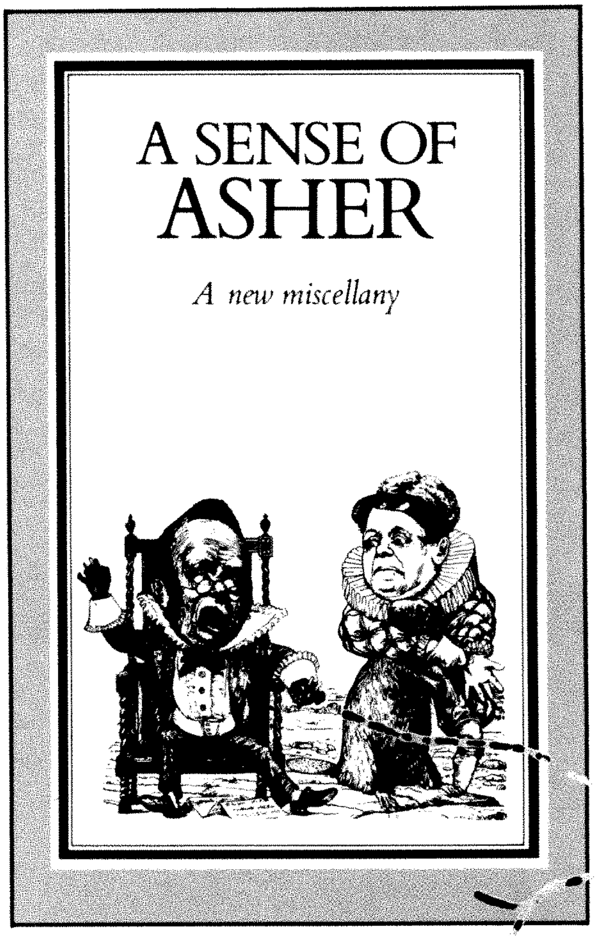

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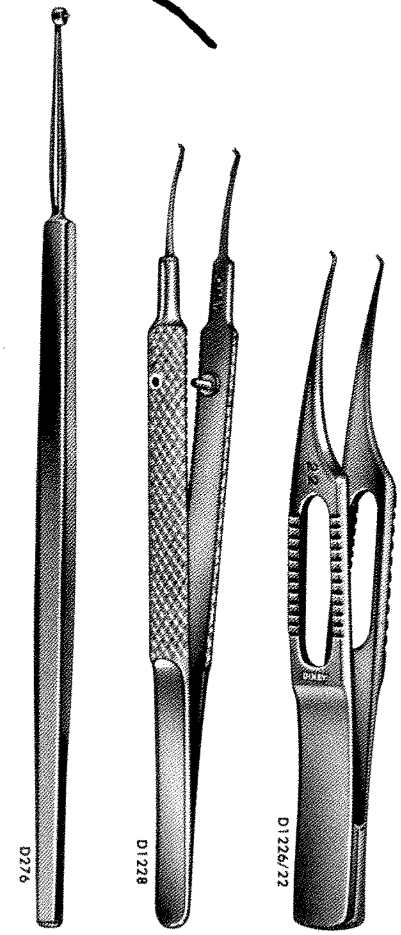

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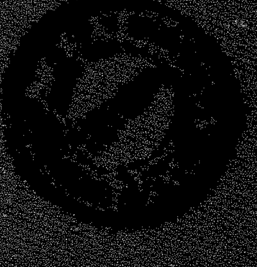

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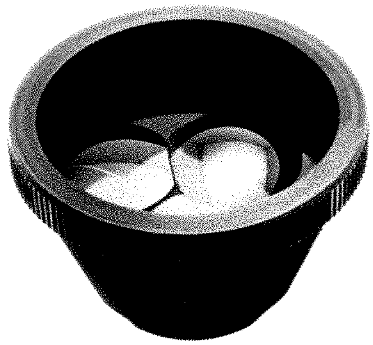

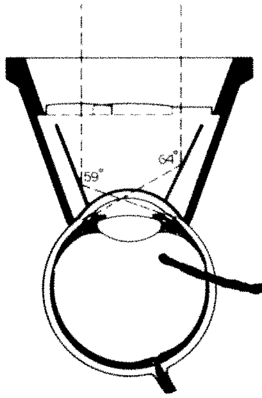

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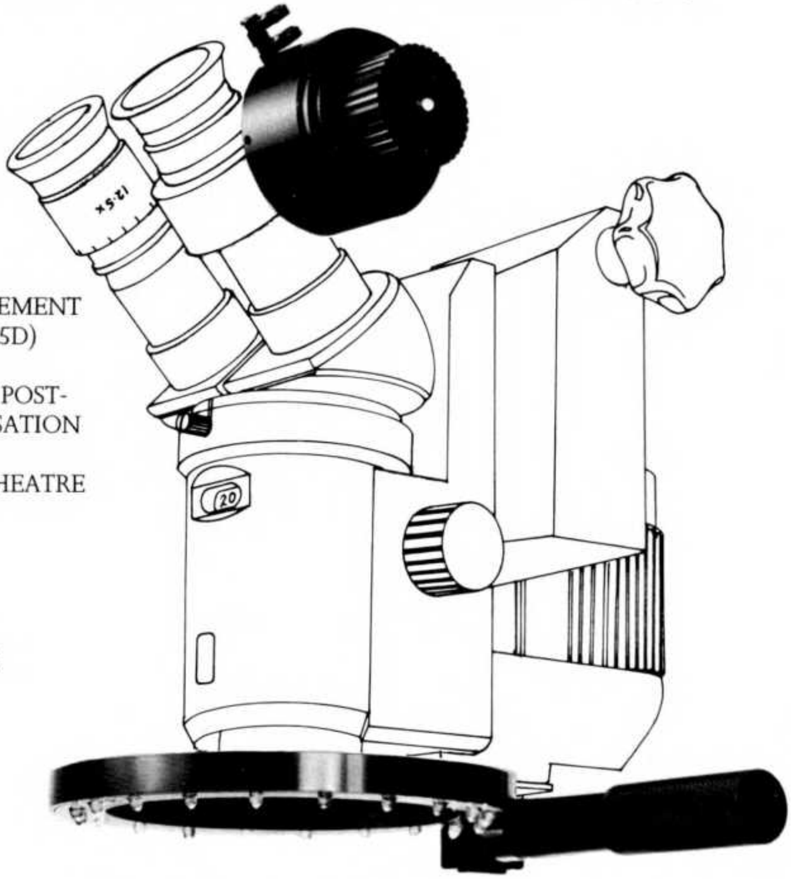

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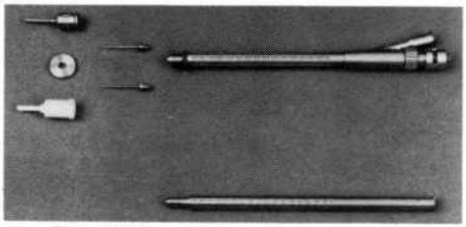

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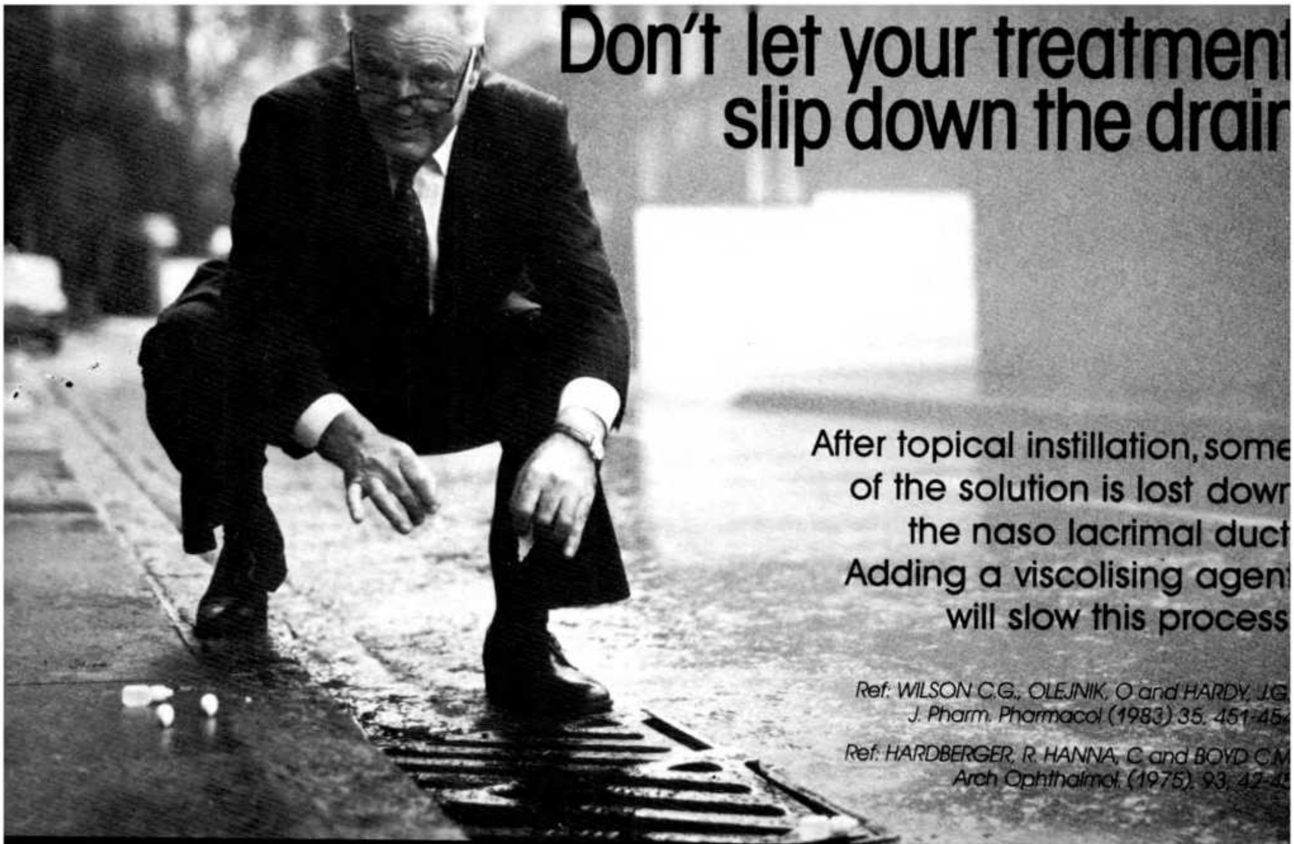

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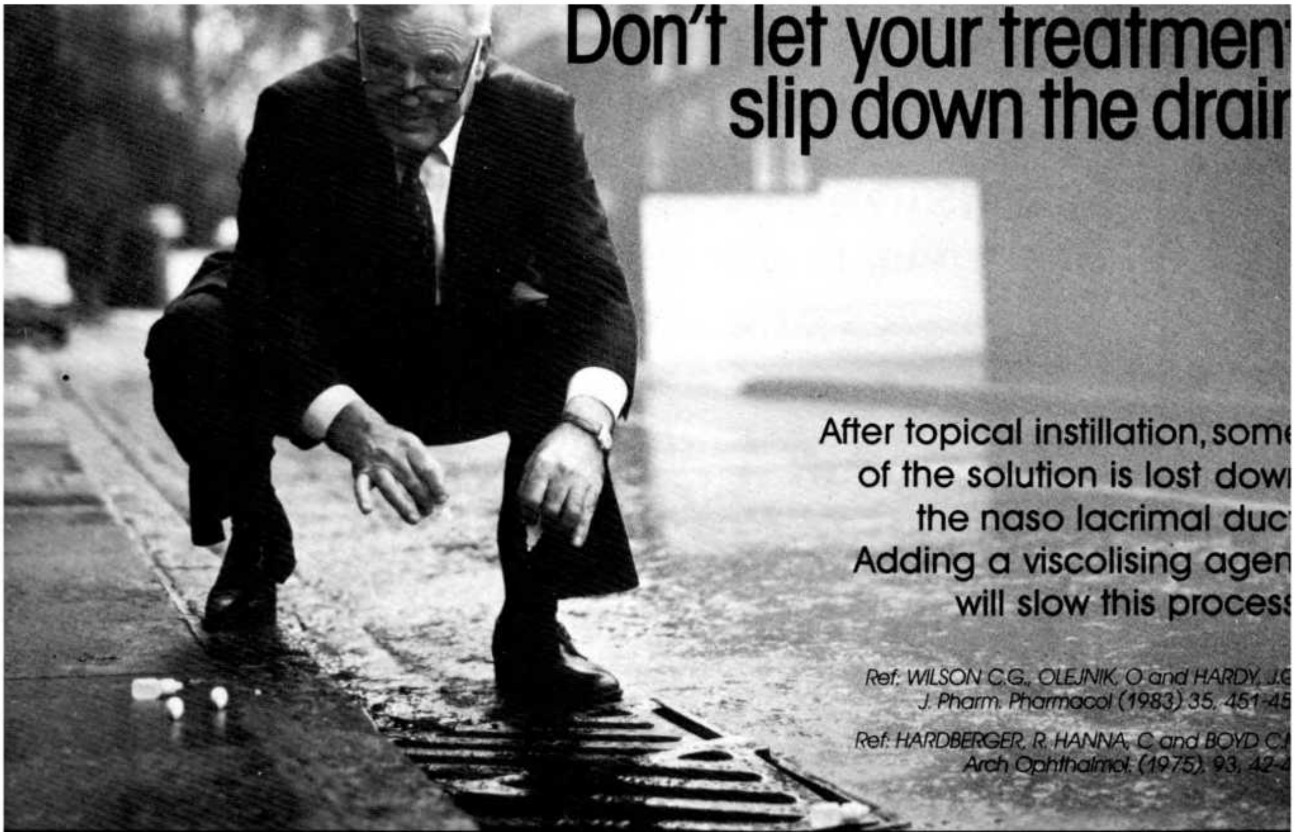

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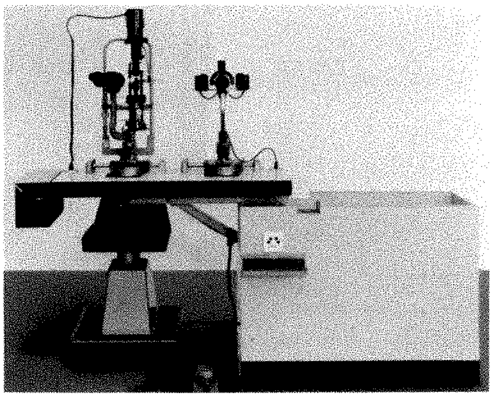

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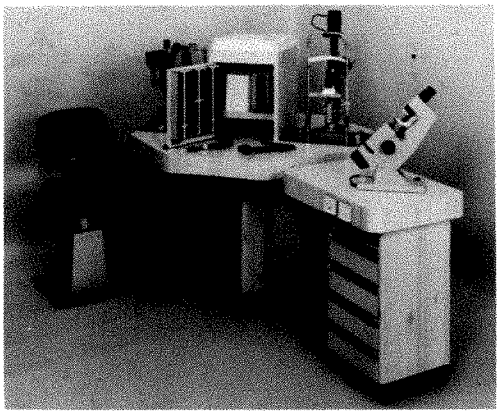

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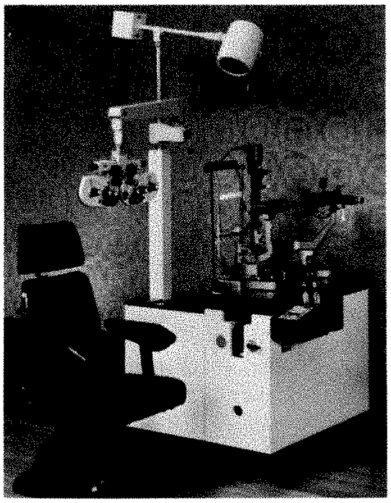

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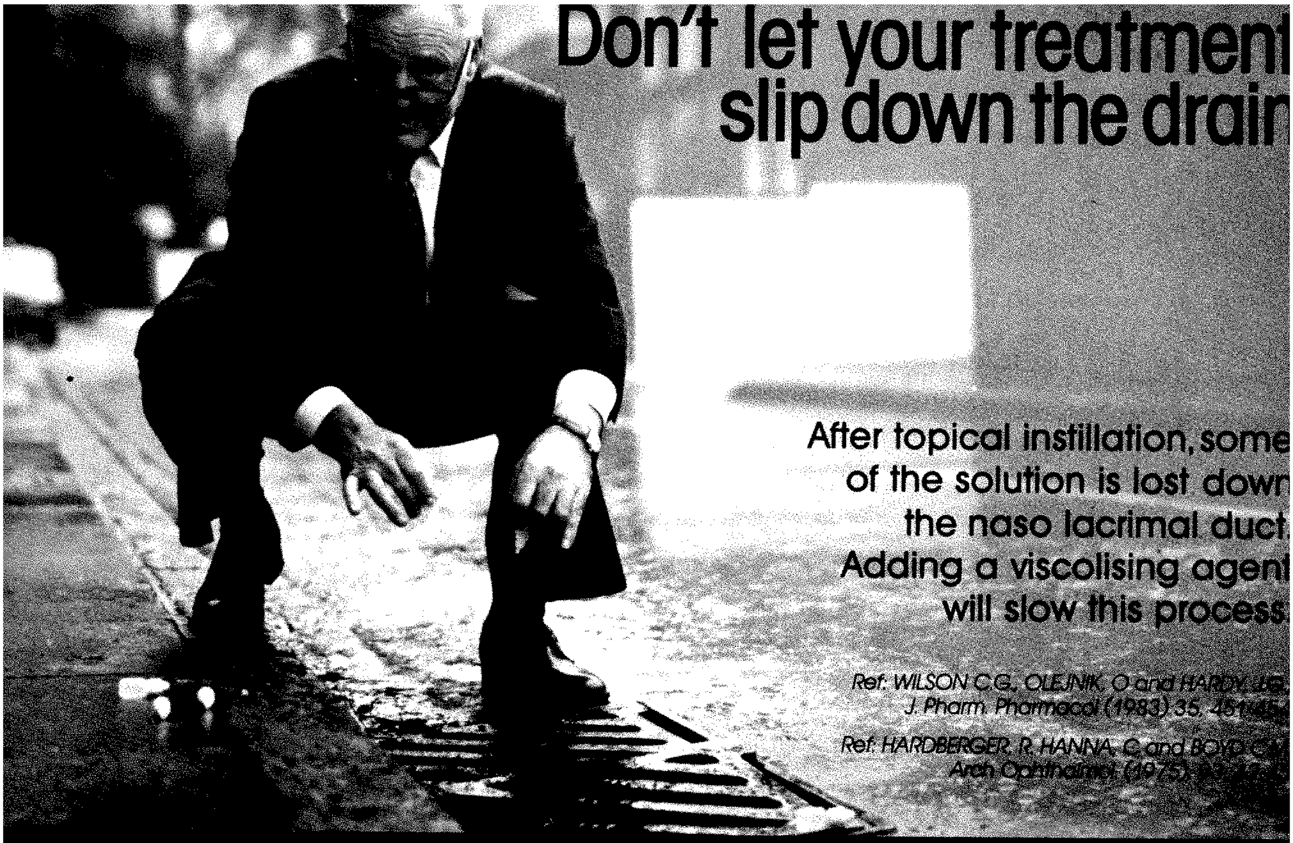

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A rapid and sensitive culture test for detecting herpes simplex virus from the eye

P WALPITA, S DAROUGAR, AND U THAKER

From the Institute of Ophthalmology, Judd Street, London WC1H 9QS

SUMMARY A rapid and sensitive culture test has been developed for detecting herpes simplex virus (HSV) in ocular infections. The virus is cultured by inoculation and centrifugation of cell monolayers grown on coverslips and the inclusions detected by an indirect immunofluorescence technique. This rapid test takes only two days to complete. By comparison, in our hands the conventional culture test, which depends on the development of cytopathic effect, took between 1 and 20 days with a mean of 4·7 days. Of the 1638 ocular clinical specimens inoculated in parallel by the two methods a total of 188 were positive for HSV. The virus was detected from 184 (97·8%) specimens by the rapid test and from 144 (76·6%) by the conventional test (McNemar's test, U=5·76, p<0·001).

Herpes simplex virus (HSV) is one of the commonest causes of corneal blindness in the developed countries. Some 300 000 cases of ocular herpes virus infections are diagnosed each year in the United States alone.[1]

In the early stage of primary HSV ocular infection, when typical lid lesions may be scanty, or in cases of HSV conjunctivitis or keratoconjunctivitis with no typical corneal lesions,[2 3] the differential diagnosis from other infections and acute allergic conditions is difficult on clinical grounds alone. In view of the potentially serious consequences of ocular HSV infection, and the fact that effective anti-HSV therapy is now available, rapid and sensitive laboratory diagnosis is essential for identifying all the various forms of this disease.

The traditional methods of laboratory diagnosis of viral infection, either by virus isolation in cell culture or by demonstration of rising antibody titre in paired sera, may take days or weeks to complete. Direct demonstration of the agent in exfoliated cells[4-6] has been tried but is generally less sensitive than cell culture, and it requires high-quality smears and strict criteria of identification of viral inclusions.

We describe here a rapid, simple, and sensitive cell culture method for the diagnosis of HSV ocular infections.

Materials and methods

Specimens. Conjunctival swabs were collected from patients attending the External Diseases Clinic at Moorfields Eye Hospital in London. The specimens were collected in plastic tubes containing glass beads and 2 SP transport medium with antibiotics[7] with the addition of 3% v/v fetal bovine serum. All specimens were stored in liquid nitrogen at −180°C for transport to the laboratory, where they were then stored at −70°C until cultured.

Cell culture and inoculation. HEp2 cell monolayers were obtained by seeding at a concentration of 25 000 to 30 000 cells/ml of growth medium in cell culture test tubes and in flat-bottomed plastic tubes containing 13 mm coverslips. Growth medium consisted of Eagle's minimum essential medium supplemented with vitamins, glutamine, antibiotics (vancomycin 100 μg/ml and streptomycin 50 μg/ml) and 10% fetal bovine serum. At the end of 48 hours' incubation, when the monolayers were approximately 80% confluent, growth medium was replaced with maintenance medium (same as growth medium but with only 3% fetal bovine serum).

Each specimen was whirlimixed and an equal volume inoculated into one test tube and one flat-bottomed tube containing the cell monolayers. Positive and negative controls were inoculated with each batch of tests.

Correspondence to Dr P Walpita.

Table 1 *Comparison of the steps involved in the rapid culture test and the conventional tissue culture test*

Rapid culture test	*Conventional tissue culture test*
1. Cell monolayer on coverslip in FBT 2. Inoculation 3. Incubation 2 days 4. IF staining	Initial inoculation: cell monolayers in TT inoculation incubation 7 days examine for CPE
Course of test 2 days	1st pass: incubation 7 days examine for CPE
	2nd pass: incubation 7 days examine for CPE IF staining of smears from test tubes showing CPE
	Course of test up to 21 days

Conventional cell culture test. The inoculated test tubes were rolled at 35°C and examined every day for the development of cytopathic effect (CPE). Smears were made from all test tubes showing CPE and the virus identified by an indirect immunofluorescence test (IF). All negative cultures were passaged at weekly intervals before being discarded at 21 days. The individual steps involved in the test are shown in Table 1.

Rapid culture test. The inoculated flat-bottomed tubes were centrifuged at 15 000 *g* for one hour and then incubated at 35°C. After 48 hours incubation the coverslips were fixed in methanol for 10 minutes at room temperature and stained by IF. The individual steps of the rapid test are shown in Table 1.

Immunofluorescence staining method. Group specific anti-HSV serum raised in rabbits in our laboratory and anti-rabbit IgG conjugated with fluorescein isothiocyanate (Wellcome Reagents Ltd) were used for staining HSV. Optimum working dilutions were determined by previously titrating each batch of reagents.

Coverslips were mounted on a staining frame, covered with a drop of the appropriately diluted anti-HSV serum, and incubated in a humid chamber at 35°C for half an hour. The coverslips were then thoroughly washed in phosphate buffered saline at pH 7·3 for 15 minutes by means of a magnetic stirrer. They were air-dried, covered with fluorescein conjugated anti-rabbit serum, and incubated and washed in buffered saline as before. They were finally washed in distilled water for five minutes before being dried and mounted in buffered glycerol. The coverslips were examined for the presence of inclusions at a magnification of 160 times under a standard 18 UV Zeiss microscope with filter set 10. The quality of inclusions was checked under high power (×400).

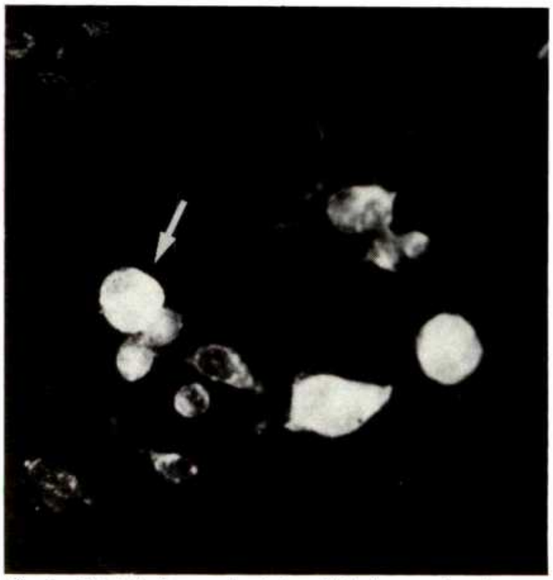

Fig. 1 *Brightly fluorescing intracellular herpes simplex virus inclusions stained by an indirect immunofluorescence method. (×540).*

The criterion of positivity was the detection of one or more brightly fluorescing granular inclusions within intact cells (Fig. 1). The quality of IF reagents was controlled by including positive and negative control coverslips in each batch of tests.

Results

A total of 1683 ocular clinical specimens were inoculated in parallel by both the rapid test and the conventional cell culture test. Correlation of positivity between the two tests is shown in Table 2. HSV was detected by either or both tests in a total of 188 specimens. Of these, 184 (97·8%) were positive by the rapid test and 144 (76·6%) by the conventional test (Table 2). The difference in sensitivity between the two tests is statistically significant (McNemar's test, U=5·76, p<0·001).

Table 2 *Correlation of positivity for ocular HSV by the rapid test and conventional test*

Results of paired tests	*Number (%) of specimens positive for HSV isolation*
Nos. positive by either or both tests	188 (100)
Nos. positive by rapid test	184 (97·8)
Nos. positive by conventional test	144 (76·6)
Nos. positive by both tests	140 (74·5)
Nos. positive by rapid test only	44 (23·4)
Nos. positive by conventional test only	4 (2·1)

McNemar's test (rapid test vs. conventional test), U=5·76, p<0·001.

Table 3 *Day of first appearance of cytopathic effect in 144 ocular HSV-positive cultures by the conventional test*

Day	*Nos. showing CPE (%)*
1	26 (18·06)
2	38 (26·4)
3 to 7	57 (39·6)
8 to 14	19 (13·19)
15 to 21	4 (2·78)

Mean=4·7 days, SD 3·6 (range 1–20 days).

The number of days taken to develop CPE in the conventional test varied from 1 to 20 (Table 3). Only 44% of the HSV positive specimens showed CPE at day 2 and as many as 16% took eight days or longer.

Discussion

We have developed a rapid culture test for HSV isolation from ocular infections and found it to be considerably faster and significantly more sensitive than the conventional cell culture test. It took far fewer steps to complete and was therefore less expensive.

In this study we have used HEp2 cells which are known to be sensitive for HSV isolation.[8] The HSV isolation rate by the rapid test was 21% higher than the conventional test. This is probably due to the increased contact and penetration of the virus into cells resulting from centrifugation. In a previous study[9] we found that centrifugation at 15 000 *g* can significantly increase the sensitivity of the cell culture for HSV isolation.

In a pilot study we compared the sensitivity of the rapid test at 24, 48, and 72 hours of incubation. The sensitivity of the test was similar at 72 and 48 hours but marginally lower at 24 hours. Because of this we chose 48 hours as the optimal incubation period.

In our hands the IF staining of HSV in cell culture proved to be entirely satisfactory. The antisera we used were highly specific, and each batch was titrated for optimum working dilution. Positive and negative controls were set up with each batch of tests to control the quality of cell culture and staining. The distinction between positive and negative reaction was clear cut (Fig. 1). The positive cultures produced brightly fluorescing, granular, and intracellular inclusions. Such inclusions were not found in negative controls. Our previous work has shown that, when the strict criteria of culture staining and recognition of inclusions are adhered to, the finding of even one such inclusion is adequate for a positive diagnosis and that the chances of a false positive in the rapid test are remote (unpublished observations).

The rapid test was completed in only 48 hours, whereas the conventional test took between 1 to 20 days, with a mean of 4·7 days. It is widely believed that HSV grows rapidly in various cell lines and that most positives show CPE within 48 hours. However, there is little reported evidence to support this belief. In a study by Moore,[10] where a large proportion of the specimens were from vesicular lesions with an expectedly high virus titre, only 72% of the HSV positives were detectable at day 2. In our study HSV was detected in the conventional test in only 44% of the positive specimens within two days, and 16% took more than seven days to develop CPE (Table 3).

The results of this study show that the rapid culture test is much simpler, faster, and less expensive, and significantly more sensitive than the conventional culture test for detecting HSV from ocular infections.

We are grateful to the staff of the External Diseases Clinic and Casualty Department, Moorfields Eye Hospital, for the collection of specimens.

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Rapid, reliable diagnosis of chlamydial ophthalmia by means of monoclonal antibodies

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SUMMARY The use of fluorescein-conjugated monoclonal antibody (Syva, UK) provided a rapid reliable diagnostic test for *Chlamydia trachomatis* in conjunctival samples from 100 adults with acute follicular conjunctivitis and seven babies with suspected chlamydial ophthalmia neonatorum. Elementary bodies (EBs) were seen in smears from 11 of the adults, and culture confirmed *C. trachomatis* infection in nine of them. Both tests were positive with specimens from four of the neonates. No specimens from either group of patients produced a negative result in the smear test but a positive result by culture. However, the two adult patients with chlamydial ophthalmia who had negative cultures but were EB-positive had both had prior topical tetracycline therapy.

Acute follicular conjunctivitis is a common problem in general practice and eye casualty departments. Many cases will be due to adenovirus infection and may resolve with symptomatic therapy. An important minority of cases, however, will be due to infection with oculogenital strains of *Chlamydia trachomatis*, when there may be concurrent (often asymptomatic) genital infection for which there is specific therapy.

Definitive diagnosis of conjunctival infection with *C. trachomatis* may be made by detecting inclusions in conjunctival cell scrapings or by isolating the organism in cell culture.[1-3] The latter method is more sensitive, but as chlamydiae are labile care must be taken with storage and transport of specimens to the laboratory. In addition isolation of chlamydiae in cell culture requires experience and constant control of sensitivity. Specimens are inoculated into McCoy cell cultures, and after 48 or 72 hours chlamydial inclusions are stained with Giemsa (or iodine) reagent.

Direct demonstration of inclusions in conjunctival scrapings stained with Giemsa provides a result within an hour of the specimen arriving at the laboratory, but it is a less sensitive method than culture. In proved chlamydial eye infections Giemsa staining of conjunctival smears detected up to only 60% of cases, and fluorescent polyclonal antibody staining detected 80%.[3,4] However, very few inclusions are found even by the fluorescent antibody technique, so that often a prolonged search for the agent is necessary.

The ability to detect reliably extracellular elementary bodies (EBs) directly in conjunctival smears would obviate both the need for culture and its associated problems, and the laborious search for inclusions in conjunctival scrapings. Recently a fluorescein-labelled monoclonal antibody specific to *C. trachomatis* has become available and allows the more numerous EBs to be detected rapidly. This technique has been shown to be sensitive and specific, when compared with isolation, in detecting chlamydiae in specimens from the genital tract (urethra, cervix).[5,6] The monoclonal antibody recognises specifically the major outer membrane protein (MOMP) of all 15 serovars (immunotypes) of *C. trachomatis*—that is A, B, and C, causing trachoma, the oculogenital strains (D–K), and L1–L3 causing lymphogranuloma venereum—but it does not cross-react with *C. psittaci*.[7]

Patients and methods

PATIENTS

One hundred adult patients with acute follicular conjunctivitis and seven babies with ophthalmia neonatorum were studied. Younger adult patients

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under the age of 35 years were selected preferentially, though some older patients were included. All patients were asked about genitourinary symptoms and all had slit lamp examination. If possible swabs were taken from both conjunctivae whether or not they were considered to be diseased. Rapid detection of *C. trachomatis* EBs was not performed, but casualty officers were informed within a few days of patients with positive direct smear results. These patients were requested to see one of us (DAH) at the Praed Street Clinic for full investigations, including genital tests. Sexual contacts were requested to attend. Blood was also taken for chlamydial serology (microimmunofluorescence test).[8] Patients were then treated with systemic tetracycline or erythromycin.

The seven babies were seen at Northwick Park Hospital and had a diagnosis of suspected chlamydial ophthalmia. The majority had had prior topical therapy (usually chloramphenicol) for their sticky eyes. The mothers (and their sexual partners) of the chlamydia-positive babies were referred for genital tests and subsequent therapy.

MONOCLONAL ANTIBODIES

These were obtained from Syva UK (Maidenhead, Berks). Conjunctival smears were examined by the Microtrak *Chlamydia trachomatis* direct fluorescent antibody reagent. Control preparations were obtained from Syva UK.

PREPARATION OF SMEARS

Eye swabs were obtained by everting the lower lid and firmly drawing an ENT swab (MW 142; Medical Wire and Equipment Co., Corsham, Wilts) along the tarsal conjunctiva. Genital material was obtained as described previously.[5]

A smear was made by rubbing the swab immediately it had been taken firmly and evenly over a circumscribed uncoated area (13 mm diameter) of a microscope slide coated with polytetrafluoroethylene, so that some material was visible on the slide. The smear was allowed to dry and then fixed immediately by covering the area with methanol (or acetone); this was allowed to evaporate without the slide being moved. Fixed smears were then stored in covered slide boxes at 4°C until transfer to the laboratory.

CHLAMYDIAL ISOLATION

After a smear had been made, the same swab was immediately agitated vigorously and expressed in 1·0 ml of sucrose-phosphate (2SP) medium with antibiotics. This was snap frozen and stored in liquid nitrogen. Chlamydiae were isolated subsequently in cycloheximide-treated McCoy cells as described previously.[9]

STAINING AND EXAMINATION OF SMEARS

Before being stained with monoclonal antibody fixed smears that had been refrigerated were allowed to reach room temperature. 30 μl of the Microtrak direct monoclonal antibody were spread over the smear and the slide was incubated at 37°C for 15 min in a moist chamber. Excess reagent was then removed by immersing the slide in distilled water, followed by a 5 min wash with stirring. After being dried the smear was mounted under a coverslip with Microtrak chlamydia direct specimen mounting fluid and examined with a Nikon L-ke microscope fitted with an epifluorescence attachment.

All the smears were coded and then read by one observer (BJT), who also examined coded Giemsa-stained McCoy cell monolayers at a later date. All

Table 1 *Demonstration of chlamydiae by direct test and culture in adult patients with conjunctivitis at presentation*

Study no.	*Sex*	*Eye*	C. trachomatis *detection*		
			Direct	*Culture*	
			IF	*Giemsa stain*	*Monoclonal antibody (CC)*
7	M	L	+++	+++	++++
		R	NT	NT	NT
41	M	L	+++	+++	+++
		R	–	–	–
44	F	L	±	–	–
		R	–	–	–
46	F	L	+++	++	+
		R	+	±	–
49	F	L	–	–	–
		R	+	–	–
61	M	L	+	++	++
		R	–	–	–
67	M	L	+++	++++	+++
		R	++	++	++
78	F	L	NT	NT	NT
		R	+	+	–
80	M	L	NT	NT	NT
		R	+	+	+
83	M	L	+++	+	++
		R	NT	NT	NT
104	M	L	++	+	++
		R	–	–	–

All other patients had negative IF/Giemsa/CC at initial visit and were not further tested.

IF=Immunofluorescence. CC=Culture confirmation. NT=Not tested.

±=1–10.
+=11–100.
++=101–1000.
+++=1001–10 000.
++++=>10 000.

The above ranges (± to ++++) apply to elementary bodies seen in the direct test or inclusions seen in cell monolayers when the culture technique is used.

Table 2 *Patient 67: male, aged 33*

Date	*L Eye*		*R Eye*		*Urethra*			*Therapy*
	IF	*Cult*	*IF*	*Cult*	*IF*	*Cult*	*PMNL*	
1 Dec 1983								Topical chloramphenicol 1/52
8 Dec 1983	+++	++++	++	++	NT	NT	NT	Topical tetracycline
9 Dec 1983	++	+	+	–	++	+++	40	Systemic doxycycline
16 Dec 1983	–	–	–	–	–	–	15	
23 Dec 1983	–	–	–	–	–	–	0	

Casual sexual partners four to six weeks previously in Phillipines. Three weeks bilateral follicular conjunctivitis Two weeks dysuria and urethral discharge. Topical chloramphenicol for one week to both eyes prior to initial testing. Wife examined and found to have chlamydial mucopurulent cervicitis

PMNL=polymorphonuclear leucocytes. For symbols see Table 1

specimens for attempted isolation of chlamydiae were processed by one person (RTE), who also examined coded McCoy cell monolayers by a culture confirmation (CC) technique using fluorescein-labelled monoclonal antibody (Syva) to detect inclusions rather than by Giemsa staining.

Results

DETECTION OF CHLAMYDIAE DIRECTLY IN SMEARS OR BY CULTURE (GIEMSA STAINING OR CC)

Adults

EBs were detected in the conjunctival smears of eleven (11%) of the adult patients. Nine of these were subsequently confirmed by culture (Table 1). Both of the two culture-negative patients had had prior topical tetracycline therapy (see below). The remaining 89 patients whose specimens were negative in the direct smear monoclonal antibody test were also culture negative.

Seven of the 11 patients who had positive direct tests had both eyes swabbed; bilateral infection with chlamydiae was found in two of these. No clinically unaffected eyes were positive. Seventy of the 100 adult patients had both eyes swabbed, making a total of 170 specimens. Taking culture as reference, this gives a specificity of 99% and a sensitivity of 100%.

Genital tests. Five of the 11 patients whose eye swabs were positive by the direct smear test defaulted after their first visit; one of these had received systemic tetracycline. The other six were contacted and agreed to be seen at the Praed Street Clinic for further assessment. While waiting for this appointment all had topical tetracycline therapy for their eye infections. The results of eye and genital tests from two of these patients are shown in Tables 2 and 3.

Effect of therapy on direct test and culture

Topical treatment. Topical tetracyclines appear to have a greater effect on culture than on the direct test. Thus a smear from the right eye of patient 49 contained 10-100 EBs while the culture was negative. This patient had been using tetracycline and Albucid (sulphacetamide) eye drops for 10 days prior to her presentation. Consequently the EBs seen may not have been viable. Unfortunately the patient defaulted, so that the follow-up genital tests were not possible. The other culture-negative patient (no. 44) had fewer than 10 EBs in a conjunctival smear from her left eye and had also received prior topical tetracycline therapy (tetracycline ointment for two weeks). Patient 67 had both eyes positive by both tests from

Table 3 *Patient 46: female, aged 24*

Date	*L Eye*		*R Eye*		*Cervix**		*Therapy*
	IF	*Cult*	*IF*	*Cult*	*IF*	*Cult*	
3 Nov 1983							Topical chlor-amphenicol
17 Nov 1983	+++	+++	+	±	NT	NT	Topical tetracycline
24 Nov 1983	++	++	±	+	+	±	Systemic doxycycline
25 Nov 1983	++	+	±	±	NT	NT	
30 Nov 1983	+	–	–	–	NT	NT	
6 Nov 1983	–	–	–	–	–	–	

Casual partner two months previously in Turkey Conjunctivitis for one month prior to presentation No genital symptoms Topical chloramphenicol for latter two weeks Progressive clinical improvement with systemic doxycycline

*Rectal and throat tests also positive

samples taken at presentation. One day later, however, after topical tetracycline therapy chlamydiae were not isolated by culturing specimens from the right eye, although >100 EBs were shown by direct immunofluorescence (Table 2).

Systemic treatment. Attempts to visualise EBs directly and to culture chlamydiae in cell culture from genital and eye sites were unsuccessful after one week or more of systemic tetracycline therapy. In one patient (no. 46), however, 10-100 EBs were seen after six days in a specimen from what had been a severely affected left eye, but the result of culture was negative (Table 3). Presumably these were dead EBs.

NEONATES

EBs were detected in the conjunctival smears of 4 (57%) of seven babies with suspected chlamydial conjunctivitis. *C. trachomatis* was cultured in every case and, conversely, the micro-organism could not be cultured in the three smear-negative babies. One of these positive smears had fewer than 10 EBs, whereas the other three had more than 100.

MICROIMMUNOFLUORESCENCE SEROLOGY

This was performed only on patients who had genital tests. All except patient number 44 were positive with IgG titres (against pooled D-K, lymphogranuloma venereum antigens) ranging from 1:16–1:128.

Discussion

The results of the study show that conjunctivitis caused by oculogenital strains of *C. trachomatis* can be diagnosed rapidly and easily by staining conjunctival smears with a fluorescent monoclonal antibody.

The conjunctival swabs were taken by a number of different medical and nursing staff in a busy eye casualty department. Nevertheless, samples from clinically affected eyes usually contained sufficient epithelial cells to indicate that they were adequate for testing. On the few occasions when inadequate smears were provided they were readily identified, and additional specimens were requested if this was clinically indicated. Eye specimens produced few non-specifically staining artefacts compared with genital specimens and so were easy to interpret. We considered as artefacts any fluorescing particles which did not have the characteristic EB morphology, colour, and brightness.[5 10] Subsequent to this study we have looked at a number of conjunctival smears taken soon after patients had applied ointment based preparations. These smears were covered with numerous fluorescent globules, which could not be confused with EBs, but made the search for small numbers of them more difficult.

The fluorescent monoclonal antibody test for EBs was at least as sensitive as routine cell culture for detecting chlamydial eye disease. It was also highly specific, though patient 44 had negative genital tests and microimmunofluorescence serology, so that the result in her case may have been a false positive.[11 12] All the eye samples found to be negative by the monoclonal antibody test were confirmed as negative by culture. The high specificity and sensitivity of the test support our claim that the technique is reliable. This does not surprise us considering previous reports of success with samples from the genital tract.[5 6]

Although the prevalence of chlamydial ophthalmia in the United Kingdom is unknown, in a large study over five years (1976–80) 18% of new patients attending the Keratoconjunctivitis Clinic at Moorfields Eye Hospital were diagnosed as having adult chlamydial ophthalmia.[1] However, in a recent study from the same hospital of 142 consecutive patients with acute conjunctivitis only 7 (5%) of the patients had chlamydial infection confirmed by culture, though serological evidence suggestive of infection was found in another 5 (4%) of the patients.[13] Ours was not a prevalence study, but the positivity rate, despite some selection, was only 11%. It is probable that this rate was reduced by an adenovirus epidemic at the time of the study. As noted by others, patients with chlamydial ophthalmia could not be readily identified by history and examination. Positive patients were not necessarily particularly promiscuous, and many had asymptomatic genital infections.

The use of the monoclonal antibody technique to diagnose chlamydial eye disease has obvious advantages. First, the problems of storage and transport of specimens associated with an isolation service in a distant laboratory are eliminated. Second, selected patients, for example neonates with conjunctivitis, can be offered a very rapid service, with results available within 30 minutes of the specimen reaching the laboratory. Third, the test is relatively painless compared with conjunctival scrapings (the other method with which rapid results can be obtained). Finally, the combination of a quick and reliable technique will allow the early identification of those patients who require systemic therapy for both eye disease and genital tract infection.

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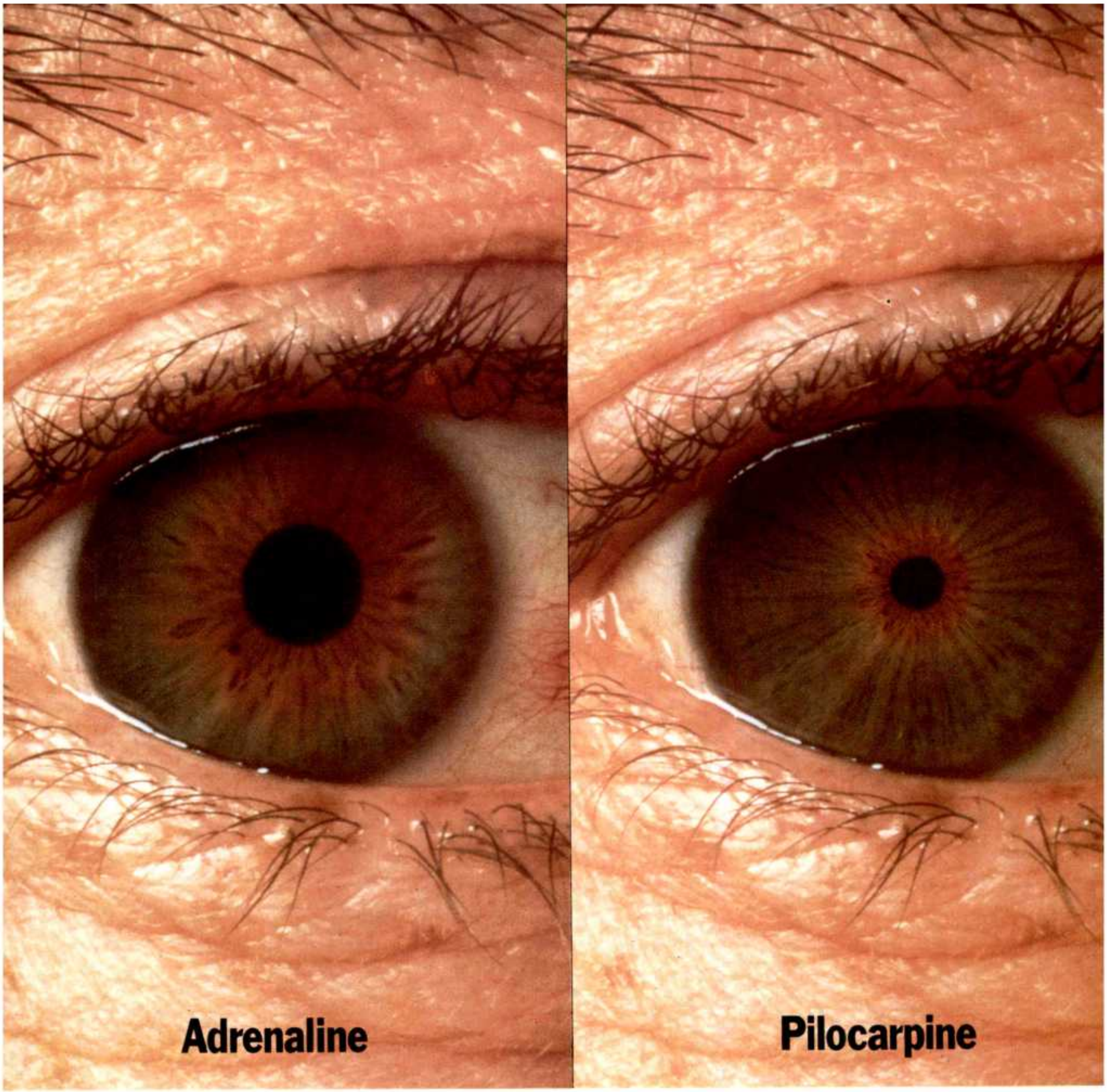

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Treatment of experimental lens capsular tears with intense focused ultrasound

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SUMMARY High-intensity focused ultrasound was employed to seal lens capsular tears in a rabbit model. Ultrasound therapy was applied either contiguously, thereby completely covering the tear, or in a discrete exposure pattern around the tear. Both methods prevented the formation of a generalised cataract. This was in contrast to results observed in a group of control (untreated) animals which all developed generalised lens opacities. Each control animal also developed a local lens opacity at the site of the capsular tear, as did half the animals treated with the discrete pattern. No animal treated with contiguous exposures developed any local or generalised traumatic-type cataract other than the small lens opacity immediately produced by the treatment. These treatment cataracts would not constitute a significant impediment to vision so long as they did not fall on the visual axis.

Mechanical injury to the human lens capsule usually results in the formation of a lens opacity at the site of damage. This local cataract typically progresses to complete opacification of the lens. Rarely the lens capsule may heal, leaving an opacity that remains confined to the region of the capsular rupture. Early removal of the lens is accepted therapy for such an injury, since retrospective studies have shown that its late removal has a higher morbidity.[1-3] Fibrin derivatives have been used as a tissue 'adhesive' to repair lens capsule perforations with some success.[4 5] We have explored a different approach using intense focused ultrasound (IFU). We now have considerable experience with ultrasound-induced lesions in the eye, both in humans and in animals. In this department we have used IFU to treat a variety of diseases including glaucoma, tumours, and vitreous membranes.[6-8] We have found that with proper care and a well designed system the technique is easy to use and has a low incidence of side effects. It also has the advantage of being non-invasive and can be performed outside the operating room.

A number of investigators[9-11] have studied cataracts produced with high-intensity ultrasound. These cataracts remained stable with time and did not progress to generalised opacification of the lens. The aim of this study was to evaluate whether a lens capsular rupture could be sealed with IFU and thereby prevent the formation of a generalised cataract. If successful this type of treatment might be beneficial either alone or in combination with fibrin glue techniques.[4 5] It might also prove useful as a palliative measure to reduce inflammation from exposed lens material.

Material and methods

Thirteen Dutchbelt rabbits were anaesthetised (Ketamine 100 mg and xylazine 15 mg intramuscularly). One pupil was dilated with phenylephrine hydrochloride (10%) and the cornea anaesthetised locally with proparacaine hydrochloride (0·5%). A 30 gauge needle, introduced through the limbus into the anterior chamber, was used to puncture and then to tear the anterior lens capsule. This manoeuvre produced either a narrow 4 mm anterior capsular tear or a gaping lesion up to 4 mm in diameter (Fig. 1).

Five rabbits served as controls. The lens of one eye of each animal was prepared as above but received no further treatment. The lenses were examined and photographed twice weekly over a 90-day period.

Eight rabbits received ultrasonic treatment approximately 30 minutes after capsular injury. The anaesthetised rabbits were prepared for immersion

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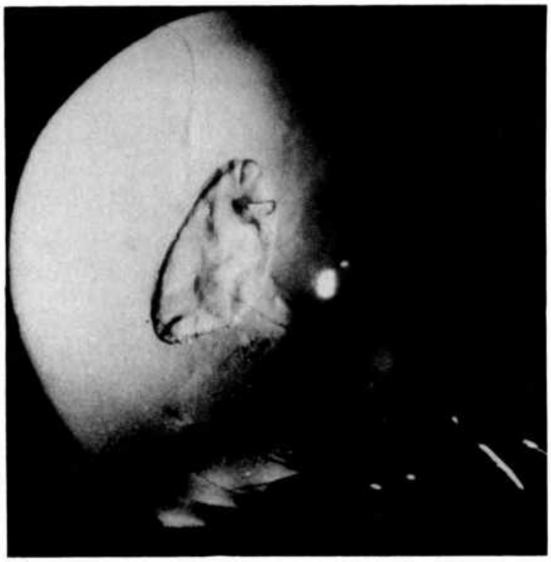

Fig. 1 *Anterior capsular tear immediately after injury.*

ultrasonic therapy in a manner previously described.[12] The ultrasound transducer was then inserted into the coupling saline solution bathing the globe, and multiple small cataracts were induced in the lens so as completely to cover the laceration. The extent of the lesions could be assessed from the opacified region of the lens. In one series of treatments (contiguous type) the lesions did overlap, but in the second series (discrete type) the lesions did not overlap (Fig. 2). Since each capsular tear varied in size and shape, 12-45 ultrasonic lens opacities were required to cover the tear. After treatment the animals were examined periodically over 90 days.

The transducer assembly[13] was a triaxial unit which held a therapeutic transducer with a central aperture. A diagnostic transducer was located within the therapeutic transducer aperture. A central aiming light was used for azimuthal positioning. The diagnostic transducer was connected to a standard diagnostic A-scan unit (Sonometrics Ophthalmoscan) and was used to ensure that the centre of the focal zone of the therapeutic beam was located on the anterior surface

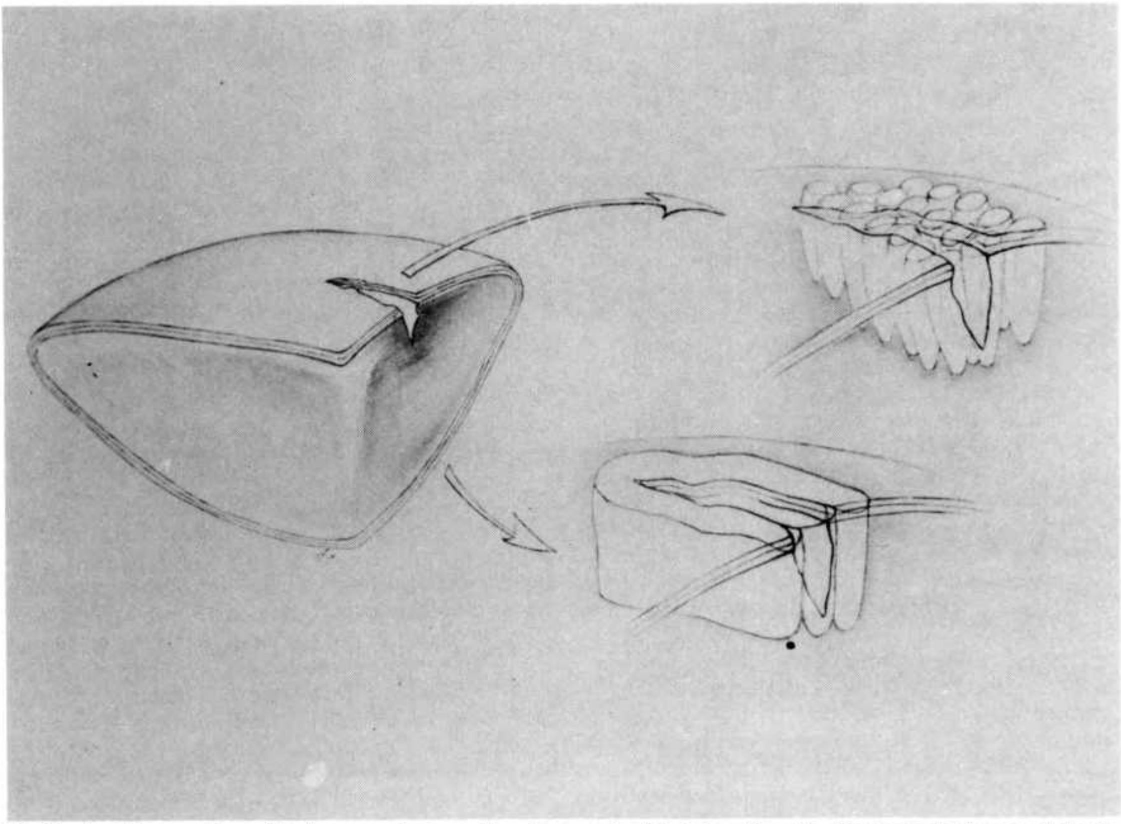

Fig. 2 *Artist's impression of the lens capsular tear with enlargements of the lesions from the discrete mode ultrasound above and from the contiguous mode of ultrasound below. In practice it was found unnecessary to place the lesions as closely as shown when using the discrete mode of ultrasound.*

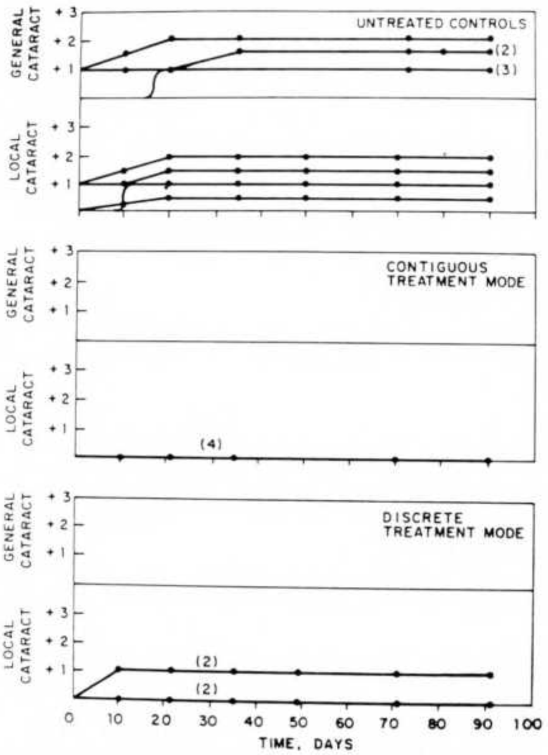

Fig. 3 *Extent and severity of lens opacities in both treatment groups and the control group and also the progression of these opacities with time.*

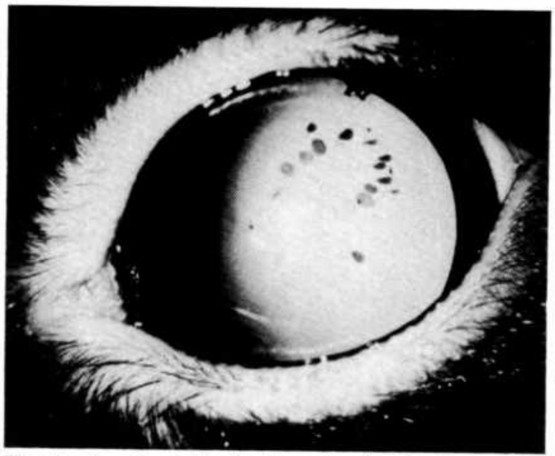

Fig. 4a *Lens treated by the discrete mode, showing individual ultrasonically induced lens opacities in an otherwise clear lens 90 days after treatment.*

of the lens (axial positioning). The resonant frequency of transducer was 1·5 MHz and in these studies it was operated at its third harmonic (4·75 MHz). At the third harmonic the half-power axial depth of focus is 3 mm and the half-power transverse width of the focal zone is 0·37 mm. In this report spatial average temporal peak (SATP) intensities are cited which refer to the SATP values within the focal plane at half-power beam width.

The lens opacities from the discrete type of treatment, which formed a row of non-overlapping lesions, were each produced with a 20 ms pulse at an intensity of 2000 W/cm^2 (SATP). Under the contiguous type of treatment the lens opacities, which form a complete blanket of lesions, were formed with 20 ms pulses generated at 10 pulses per second at the same intensity level.

Results

All cataracts resulting from the capsular injury were categorised as 'local' or 'general' according to whether they were localised to the tear or had spread into the entire lens. They were also graded as to degree (slight (+1), moderate (+2), severe (+3)). Although these gradations are not quantitative, they did allow qualitative comparison of various lesions over the 90-day period.

Fig. 3 shows the results for the untreated control group, the group receiving the contiguous mode of therapy, and the group receiving the discrete mode of therapy. The incidence of generalised and localised cataract is shown for each treatment group together with a qualitative estimation of its degree and time relationship to the lens capsular rupture. It is seen

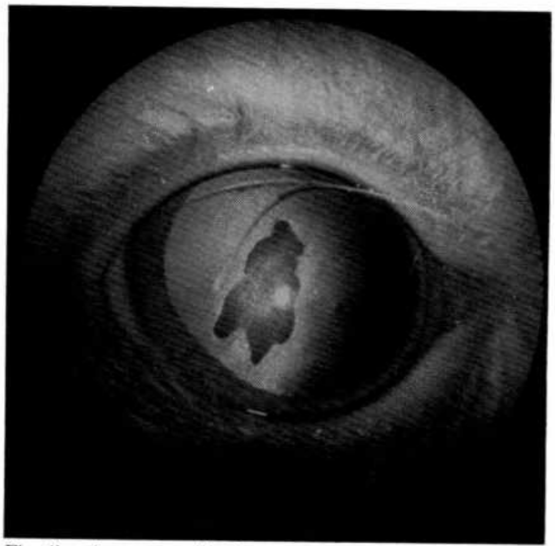

Fig. 4b *Lens treated by the contiguous mode, showing single ultrasonically induced lens opacity 90 days after treatment.*

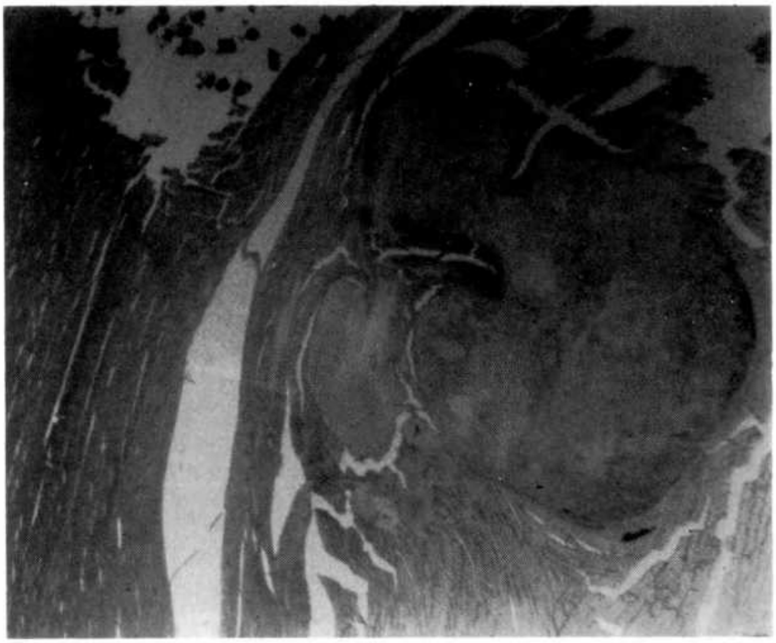

Fig. 5 *Large, discrete, irregular shaped area of homogeneous pale pink material within the ultrasonically induced lens opacity. (Haematoxylin and eosin, ×18).*

that all untreated lenses developed mild generalised cataract within three weeks. All lesions that received the contiguous mode of treatment had no local or general extensions. Two of the four lenses that received the discrete mode of treatment showed limited local extension, which stabilised after about 10 days. None of the lenses receiving the discrete form of treatment showed any general extension of the cataract induced by the capsular tear (Figs. 4a, b). In addition none of the ultrasonically induced cataracts grew in size over the study period.

Light microscopic examination of a lens treated with the contiguous mode showed the following features. In the inner cortical region the lens fibres

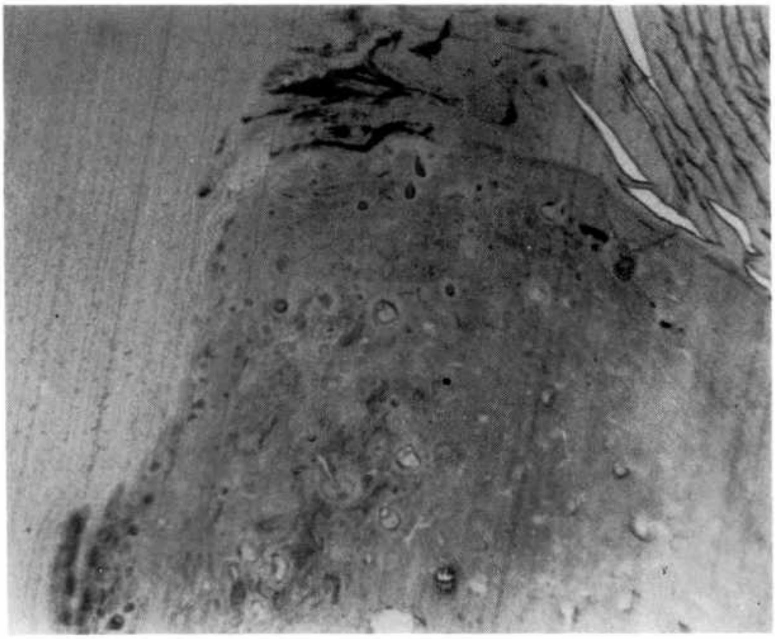

Fig. 6 *Photomicrograph: Small globular structures and granular brown pigment within the ultrasonically induced lens opacity. (Haematoxylin and eosin, ×180).*

were interrupted by large, multiple, discrete, irregular shaped areas of homogeneous pale pink appearance (Fig. 5). At the periphery of these homogeneous areas small globular structures of varying sizes were frequently seen. Within the homogeneous areas granular brown pigment was occasionally observed (Fig. 6). The lens fibres immediately adjacent to the homogeneous areas occasionally showed minimum disorganisation. The remaining lens fibres outside the treated areas appeared normal.

In a lens treated by the discrete method lenticular changes were similar to those noted above except that the lesion was smaller and more sharply delineated. It was also situated in the inner cortical zone. The lesion in this lens contained a larger amount of granular brown pigment than the other lens.

Discussion

In this animal study we have demonstrated that the development of a generalised traumatic cataract following capsular rupture can be prevented by the use of a matrix of ultrasonically induced lens opacities that are small, localised, and stable. This therapy could be used in the management of lens injury in humans. The usual treatment for a lens with a medium or large capsular rupture is its rapid removal, since generalised cataract develops very frequently. However, small through-and-through intraocular injuries due to foreign bodies may heal without cataract formation, as may small peripheral tears. Early removal of the lens is technically easier and associated with less uveitis and more rapid visual rehabilitation.[2,14] However, there are major problems associated with monocular aphakia, particularly in the very young. If an otherwise clear lens with a damaged capsule could be saved, this would offer a considerable advantage for preserving useful binocular vision. Eagling[15] found that, in seven out of eight patients under the age of 8 years with a penetrating injury involving only the lens and cornea, the visual acuity was less than 6/18 at 18 months. In comparison 65% of a group of all patients with similar injuries achieved a visual acuity of 6/12 or better. In addition 12 of her 20 patients successfully fitted with contact lenses complained of diplopia.[15]

This method of ultrasonically sealing lens capsular tears might allow retention of an injured lens if the following conditions are met. Firstly, the capsular damage must be outside the visual axis. Secondly, the time lapse between injury and ultrasonic sealing must be relatively short, probably less than 24 hours. Thirdly, the safety of the procedure needs further evaluation, particularly in respect of whether ultrasound application results in increased technical difficulties with subsequent lens removal, should this prove necessary. Further studies are needed to delineate the operative mechanism responsible for 'sealing' the lens capsular tear, to identify optimal exposure levels, and to study the long-term benefits of this procedure. The initial results are promising, and together with other advantages of ultrasonic therapy they offer prospects of a practical, easy-to-use technique.

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Retinal detachment following extracapsular cataract extraction and posterior chamber intraocular lens implantation

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SUMMARY Fourteen cases of primary retinal detachment after extracapsular cataract extraction and posterior chamber intraocular lens implantation were treated by scleral buckling surgery. Retinal reattachment was achieved in 100% of the cases. All eyes had a postoperative visual acuity of 6/30 or better; in six eyes the visual acuity was 6/12 or better. We attributed our high anatomical success rate to early detection of the retinal detachment, good visibility of the retinal breaks, lack of inflammatory reaction in the vitreous body, and preoperative absence of fixed retinal folds and preretinal membranes.

Posterior chamber intraocular lens (PC-IOL) implantation following extracapsular cataract extraction (ECCE) has recently gained much popularity among ophthalmic surgeons.[1] Although retinal detachments have been mentioned as a complication of PC-IOL implantation,[2] to our knowledge the clinical features of these cases have not been described. We have treated 14 cases of retinal detachment after PC-IOL implantation. Their characteristics and the course and result of their management are presented here.

Materials and methods

From 1979 to 1981 our group managed 122 consecutive cases of primary pseudophakic retinal detachment,[3] of which 14 occurred after PC-IOL implantation. We were not the primary surgeons for the cataract, implant, or capsulotomy procedures, and the nature of our referral practice made it difficult to obtain details on the type of IOL and the timing and surgical technique of the capsulotomy in every case.

Each patient had a complete preoperative ophthalmic examination including gonioscopy. The fundus of each eye was studied by two observers, and findings were documented in large, colour-coded fundus drawings. Scleral indentation of the fundus periphery was regularly performed, as well as dynamic vitreous biomicroscopy with a three-mirror contact lens.[4] We found the small-pupil binocular indirect ophthalmoscope very useful in detecting retinal breaks when the pupil was small,[5] and ophthalmoscopy conducted while the patient was under anaesthesia before the start of the retinal surgery in many cases revealed retinal breaks that had not been observed during the preoperative examination.

In every case the retinal breaks were treated with cryotherapy or diathermy, and buckled with an intrascleral silicone implant with encircling band. When the ora serrata was not completely visualised for 360°, or when the retinal breaks could not be detected, we performed a scleral buckling that extended over the circumference of the retinal detachment and as far posteriorly to the region where the retina was visible.[6] Radial buckles were used under circumferential buckles for retinal breaks posterior to the equator. Except in three cases (cases 4, 7, and 14), subretinal fluid was released slowly in a controlled fashion, and hypotony was minimised by simultaneous scleral indentation or, in two cases, by careful intravitreous air injection. Corneal endothelial damage caused by a large air bubble pushing

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Table 1 *Preoperative findings*

Case no	*Age (years)/ Sex*	*Symptoms/ Duration*	*Duration from IOL to detachment (months)*	*Preoperative view of fundus periphery**	*No. of retinal breaks*	*Extent of detachment†*	*Macular detachment*
1	51/M	V, F/3 wks	5	10/12‡	1	2/4	Yes
2	70/M	V/2 wks	2	12/12	1	3/4	Yes
3	71/F	F/3 days	60	12/12	3	4/4	Yes
4	51/M	None	7	12/12	1	1/4	No
5	76/M	D, F/4 days	48	12/12	1	2/4	No
6	79/F	D/1 wk	3	6/12§	1	2/4	Yes
7	61/M	None	13	12/12	1	1/4	No
8	51/M	V, D/2 wks	16	12/12	1	2/4	Yes
9	60/M	F/4 days	19	12/12	1	1/4	No
10	76/F	None	10	12/12	0	1/4	No
11	78/M	D/3 days	14	12/12	1	3/4	Yes
12	72/M	V/1 day	9	12/12	5	2/4	Yes
13	65/F	V, P/3 days	1	12/12	3	2/4	Yes
14	60/M	F/1 day	2	12/12	1	1/4	No

V=decreased visual acuity, D=defects in peripheral visual field; F=floaters, P=photopsia
*Number of clock hours of the peripheral fundus that could be clearly observed on ophthalmoscopy
†Number of quadrants of the total fundus involved ‡Caused by vitreous pigments inferiorly. §Caused by remnants of lens cortex.

the IOL against the cornea was circumvented in one case (case 3) by simultaneous anterior chamber injection of an air cushion.

Postoperatively we monitored the position of the retinal breaks on the buckle and the absorption or reaccumulation of subretinal fluid with daily indirect ophthalmoscopy. Slit lamp examination was regularly performed for early detection of anterior chamber shallowing caused by postoperative choroidal effusion.[7] Choroidal tap was considered only when medical therapy yielded no improvement in the corneal touch and the associated keratopathy. All successful cases of retinal reattachment were followed up for a minimum of six months.

Results

This study included 14 eyes (3 right, 11 left) of 14 patients (10 males, 4 females). Table 1 summarises the preoperative findings. Three patients did not present with any symptoms when the peripheral quadrantic retinal detachment was discovered on routine ocular examination. In eight cases the retina became detached within a year after the cataract surgery and IOL implantation, with four cases occurring within the first three months. A history of intraoperative vitreous loss was not elicited from any of the referring cataract surgeons. However, vitreous gel was observed preoperatively to herniate through the posterior capsulotomy and around the PC-IOL into the anterior chamber in cases 3 and 12. Posterior capsulotomy was detected in all 14 cases. On ophthalmoscopy there was no difficulty in viewing the fundus periphery except in two cases; one had heavily pigmented opacities in the inferior vitreous base, and the other had significant peripheral cortical remnants from incomplete extracapsular lens extraction. In both these eyes the inability to observe the ora serrata for its entire 360° did not compromise the success of locating the retinal breaks. In 11 of the 14 cases the detachment involved one or two quadrants of the fundus, and in six cases the macula was still attached at the time the retinal detachment was detected. In two of the eight eyes in which the macula was detached preoperatively (cases 1 and 8), the preoperative visual acuities were not profoundly depressed before the diagnosis was made. We took particular notice of the clarity of the vitreous and of the absence of preretinal membranes, full-thickness retinal folds, and star folds.

Intraoperatively, in addition to scleral buckling, intravitreous air injection was performed in two eyes (cases 3 and 13) to tamponade the retinal breaks, which were complicated by the fish-mouth phenomenon. In case 13 the retinal operation undertaken one month after the cataract operation was complicated by corneal wound leakage, which was repaired with additional corneal sutures. Retina reattachment was achieved in all 14 eyes. During the follow-up period retinal detachment did not recur, and we did not observe any signs of vitreoretinal proliferation.[8] Additional operations were performed, however, on three eyes. In case 8 the surgeon elected to reinforce the chorioretinal adhesions around the retinal break with photocoagulation in the immediate postoperative period. Choroidal effusion was observed in three eyes after the primary scleral buckling procedure. In two eyes the effusion

Table 2 *Operative findings and results*

Case no	*Concomitant procedure*	*Additional procedure*	*Preoperative visual acuity*	*Most recent visual acuity*	*Length of follow-up*	*Postoperative complication*
1	—	—	6/30	6/12	12 mos	—
2	—	—	HM at 1 meter	6/18	6 mos	—
3	Air injection	—	HM at 1 meter	6/21	6 mos	—
4	—	—	6/21	6/21	8 mos	—
5	—	—	6/6	6/12	6 mos	Pigmentary maculopathy
6	—	—	CF at 2 m	6/21	16 mos	—
7	—	—	6/7 5	6/6	13 mos	—
8	—	Laser reinforcement of retinal break	6/60	6/15	6 mos	Choroidal effusion responsive to medical therapy
9	—	—	6/9	6/12	11 mos	Pigments on IOL
10	—	—	6/9	6/15	8 mos	Cystoid maculopathy
11	—	—	HM at 0·5 m	6/21	27 mos	Cystoid maculopathy
12	—	Choroidal tap	HM at 0·5 m	6/30	15 mos	Macular pucker
13	Reinforcement of corneal wound; air injection	—	CF at 2 m	6/6	22 mos	—
14	—	Choroidal tap	6/21	6/6	6 mos	—

HM = hand movements; CF = counting fingers.

persisted despite medical therapy, and was finally relieved by uneventful choroidal tap. Table 2 lists the operative procedures, findings, and results.

At the most recent follow-up visit 10 eyes had improved visual acuity of one line or more on the Snellen chart. In one eye there was no change, and in three eyes the postoperative visual acuities were worse than the preoperative ones. In these three cases the contributing causes were pigment clumps in the macula, persistent cystoid maculopathy, and pigment dispersion on the surfaces of the IOL. None of our cases had visual acuity worse than 6/30 postoperatively, and visual acuity of 6/12 or better was achieved in six cases (43%).

Discussion

One of the proposed theoretical advantages of ECCE and PC-IOL over conventional methods of cataract extraction has been the preservation of vitreous stability in the posterior segment, minimising the occurrence of vitreoretinal traction, cystoid macular oedema, and retinal detachment.[9] Although ECCE with PC-IOL has gained much popularity among ophthalmic surgeons, it is still a relatively new procedure, and the eyes that have undergone this operation have not been followed up long enough to permit a reliable determination of the incidence of postoperative retinal detachment. The nature of our retinal referral practice does not allow us to draw from our data any conclusion pertaining to this incidence. Although the number of cases in this study is relatively small, certain trends are apparent.

Retinal reattachment was achieved in all our cases. This reattachment rate of 100% could be attributed to a number of factors. In many of our cases the retinal detachment was diagnosed and repaired before it involved the entire fundus. Perhaps patients with PC-IOLs were more aware of changes in their peripheral visual fields and more likely to seek medical attention soon after the onset of symptoms. In addition to making an earlier diagnosis of retinal detachment in most of our cases we also found no difficulty in visualising the retinal breaks. In only one eye were the peripheral cortical remnants significant enough to obstruct the view of 6 clock hours of the ora serrata, but this did not prevent locating the retinal break contributing to the detachment. The recent boom in ophthalmic technology in improving microsurgical instruments, the refined microsurgical techniques, and the increasing experience of ocular surgeons in mastering the extracapsular procedure all lead to thorough removal of peripheral lens cortex in most of these ECCE cases.

The success rate of any clinical study concerning the surgical management of retinal detachment depends on the number of cases with proliferative vitreoretinopathy[3,8] included in the study population. In our cases we were impressed by the lack of vitreous reactions both preoperatively and postoperatively. In no instance did we observe any full-thickness fixed retinal folds, preretinal membranes, or haziness of the vitreous gel. It is likely that the conditions at the time of the cataract extraction that would permit the safe implantation of a PC-IOL would also produce the least disturbance in the vitreous body during the operation and after it. Perhaps the short duration of the retinal detachment before it was diagnosed and repaired (Table 1) also contributed to the absence of preretinal membranes and therefore indirectly to the results obtained.

Thus, in this study, although we could not substantiate the claim that ECCE and PC-IOL minimise the incidence of postoperative retinal detachment, we have shown that, at least in our cases, when retinal detachment occurred in eyes following ECCE and PC-IOL, the prognosis of retinal reattachment with surgical repair could be excellent.

Records from Drs I D Okamura, J W McMeel, H M Freeman, and R C Pruett were also included in this study.

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Shifting subretinal fluid in rhegmatogenous retinal detachment

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SUMMARY In a consecutive series of 470 cases of rhegmatogenous retinal detachment 25 (5%) were found to have shifting subretinal fluid (SRF) at the preoperative examination. The study showed that the association between SRF and rhegmatogenous retinal detachment is unusual but not rare. Shifting SRF was most often associated with aphakic and longstanding retinal detachment, and found in cases in which the retinal holes were small.

The term shifting subretinal fluid (SRF) is used when after a change in posture the configuration of the detached retina, when observed with indirect ophthalmoscopy, alters immediately owing to the movement of SRF in the subretinal space to the most dependent part of the globe. Thus, with inferior shifting SRF, rotation of the patient's head from side to side results in transfer of SRF from one inferior quadrant to the other. Most rhegmatogenous detachments do not show shifting SRF, but it is frequently observed in cases of non-rhegmatogenous detachment. The latter group includes various disorders (for example, eclampsia) and inflammatory conditions such as Vogt-Koyanagi-Harada syndrome,[1] and it has also been associated with a uveal effusion syndrome with bilateral serous retinal detachment.[2] The suggestion has also been made that shifting SRF is more commonly seen where the detachment is relatively longstanding and retinal holes are small.[3] The association of shifting SRF with rhegmatogenous retinal detachment has otherwise received little attention, and the purpose of this study was to examine the clinical features of 25 cases.

Patients and methods

Four hundred and seventy patients undergoing retinal detachment surgery at St Thomas's Hospital were studied. Patients were examined routinely by binocular indirect ophthalmoscopy and scleral depression. The posterior segment was also examined with three-mirror gonioscopy. Particular details of the vitreous cavity and the detached retina were entered on proforma sheets. In order to decide whether shifting SRF was present our patients were examined in the supine and sitting positions. Observation of the fundus was made by indirect ophthalmoscopy when the head was rotated from side to side. Patients were deemed to have shifting SRF only if the movement of fluid was massive (i.e., with an obvious change in configuration of the detached retina).

Results

Twenty-five cases (5%) of our series were found to have shifting SRF.

Membranes. For shift of SRF to occur the retina must be mobile enough to allow its contour to change. Twenty (80%) of our cases had no evidence of periretinal membrane formation, and in the remaining five cases there was only minimal preretinal membrane present which was not sufficient to interfere with retinal mobility.

Holes. Of the 25 cases studied 15 (60%) were found to have retinal holes either before or during operation. In all cases the holes were 'small'—i.e., small enough to be detected with difficulty by indirect ophthalmoscopy). Holes were not found in the remainder principally owing to the significantly high ($p<0.05$) incidence of aphakia in the shifting SRF group (Table 1), with the recognised difficulty in locating small holes in these cases.[4]

Posterior vitreous detachment. In all 25 cases with shifting SRF a complete posterior vitreous detachment was present.

Duration of retinal detachment. In our series (Table 2) 17 (68%) detachments had been present for more than one month as compared with 187 (42%) in

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Table 1 *Refractive errors in the series of 470 cases*

	Shifting SRF (25)	*Non-shifting SRF (445)*
Aphakia	13 (52%)	85 (19%)
Myopia	4 (16%)	205 (46%)
Emmetropia	8 (32%)	155 (35%)

Table 2 *Duration of retinal detachment in series of 470 cases*

	Shifting SRF (25)	*Non-shifting SRF (445)*
0–1 week	1 (4%)	89 (20%)
2–4 weeks	7 (28%)	169 (38%)
1–6 months	11 (44%)	125 (28%)
More than 6 months	6 (24%)	62 (14%)

the rest of the series. This difference is significant ($p<0.05$) and indicates that detachments in the shifting SRF group were relatively longstanding.

Discussion

For shift of SRF to occur the retina must be sufficiently flexible to allow its contour to change. Thus in our 25 cases retinal fibrosis, which can result in immobility of detached retina, was either completely absent or very slight. In all our cases the retinal holes which we were able to detect were small, confirming the observation of Schepens.[3] It is probable that small retinal holes prevent rapid movement of fluid between the subretinal and retrohyaloid space, fluid tending to remain in the subretinal space. In all 25 cases complete posterior vitreous detachment was present. Complete vitreous detachment, particularly if combined with intracapsular aphakia (52% of our cases), may contribute to the aetiology of shifting SRF, as there is substantial anterior displacement of gel to allow unrestricted movement of the retina free from vitreous tamponade.

In conclusion, shifting SRF is a physical sign that can be observed in a small proportion of patients with rhegmatogenous retinal detachment (5%). It is more common in cases of aphakic and longstanding detachment and ones that have not been complicated by periretinal fibrosis. Retinal holes when found were small.

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We are grateful to Mrs Margaret Grice for her secretarial assistance.

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Changes at the periphery of a lesion in necrotising scleritis: anterior segment fluorescein angiography correlated with electron microscopy

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SUMMARY Anterior segment fluorescein angiography in scleral disease reveals highly characteristic changes in the vasculature of the anterior segment associated with necrotising scleritis. The vaso-obliterative changes discovered in this investigation have been correlated with the histopathology in a patient who had to have tissue replaced. Light and electron microscopy of scleral tissue excised from sites of vascular closure detected by fluorescein angiography peripheral to the scleral defect revealed pathological changes in the absence of inflammatory cell infiltration. These changes included vascular stasis, partial vaso-obliteration, and fibroblastic transformation of scleral fibrocytes in association with intra- and extracellular degradation of the collagenous component of the matrix.

A wide spectrum of inflammatory conditions can be recognised which affect the connective tissue coats of the eye, but not all give rise to destruction of the scleral matrix.[1,2] Clinically the inflammatory changes may be confined to the episcleral tissue alone (episcleritis) or involve the deeper scleral tissue (scleritis). The inflammation usually affects the anterior segment, but if it does extend or arise behind the equator a posterior scleritis may develop. The most serious form of scleral inflammation is necrotising scleritis in which the sclera is destroyed by the inflammatory process or becomes sequestered and later removed.

Recent studies have shown the value of anterior segment fluorescein angiography in the early detection of necrotising scleritis.[2,3] In episcleritis and in diffuse and nodular scleritis which do not give rise to destructive changes the vascular flow is rapid and the vessels readily perfused. In necrotising scleritis, however, the vascular flow is markedly reduced. If the condition persists the vessels become non-perfused. Once this has occurred reperfusion of these vessels does not take place even though the inflammation resolves. In some patients the sclera in the area of non-perfusion will necrose, ulcerate, or sequestrate. Vascular changes can be detected remote from but contiguous with those areas of scleral destruction. The purpose of this investigation was to identify the changes in the sclera which occur within those areas.

Material and methods

PHOTOGRAPHY

Colour photographs of the lesions were taken at a magnification of 10× and 16× on a Zeiss photo slit lamp with Ektachrome 64 ASA film and a diffuse light source. A camera aperture between f22 and f32 was selected depending on the amount of reflected light from the sclera.

FLUORESCEIN ANGIOGRAPHY

This was performed on the same camera using a power pack with a recycling time of one second at full output. A Zeiss blue glass filter 30:14:63 (465 nm) was placed in front of the flash source and an interferential barrier filter of 525 nm of sharp cut-off characteristics placed in front of the film. The film used was 400 ASA Ilford HP5 or Kodak Tri X developed in ID11 for 12 minutes at 68°F (20°C).

With the patient positioned on the slit lamp, two control photographs were taken at 10× or 16× before injection of dye in order to determine the

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degree of autofluorescence. Autofluorescence was minimised by adjusting either the angle of incident illumination or the intensity of the flash. The angiographic series was undertaken in darkness to exclude pseudofluorescence.

5 ml of 10% fluorescein was injected into the antecubital vein. Photographs were taken at one-second intervals beginning 10 seconds after the time of the injection, because almost all the relevant information is obtained from the very early passage of dye through the anterior segment vessels. A few photographs were also taken in the late venous phase. A yellow barrier filter routinely used over the eyepiece was omitted to facilitate observations of the very earliest dye transit. Care was exercised in precise focusing and exact alignment perpendicular to the point of interest, because of the very small depth of field available.

Late phase photographs were taken in areas remote from the site of inflammation to compare the late staining characteristics.

The results were evaluated from positive transparent contact prints.

MICROSCOPY

Tissue from the site of examination by fluorescein angiography, removed intact during the preparation of the graft bed in each of the two scleral lamellar grafts, was fixed by immersion for 2 hours at room temperature in 2·5% glutaraldehyde buffered to pH 7·2 with 0·1 M sodium cacodylate containing 3 mM $CaCl_2$. It was rinsed in buffer, postfixed in 1% osmium tetroxide, stained en bloc in uranyl acetate, dehydrated, and embedded in Araldite.

Sections approximately 1 μm thick were stained in 1% toluidine blue for light microscopy. Ultrathin sections with silver-gold interference colours, after staining in uranyl acetate and lead citrate, were examined in a Philips 201C electron microscope.

Results

CASE HISTORY

In 1976 at the age of 52 a white male agricultural worker developed rheumatoid arthritis of rapid onset. The disease progressed aggressively in spite of therapy with gold, penicillamine, azathioprine, and non-steroidal inflammatory drugs. Unfortunately he developed severe reactions to each of these drugs, and they had to be withdrawn. In 1979 the left eye became very inflamed but was not very painful. Initially there was a good response to systemic steroid, but then in December 1980 both the sclera and cornea started to ulcerate (Fig. 1). This proceeded in spite of continued high dosage steroid therapy. Laboratory investigations revealed high levels of IgG and IgM, positive results for rheumatoid factor, 1/25 antinuclear factor, and 44% immune complexes (polyethylene glycol method), and an erythrocyte sedimentation rate of 53 mm in the first hour.

Because of the progression of the lesion and his failure to respond to therapy at doses which he could tolerate, it was decided to replace the damaged tissues. At operation on 10 February 1981 a lamellar corneoscleral graft together with overlying conjunctiva was performed to include both the ulcerated area and the areas which failed to perfuse on the angiogram (Figs. 2 and 3). It was found that the conjunctiva was adherent to the episclera at this site. Tissue removed in preparation of the graft bed was processed for microscopy. The graft was covered in part with conjunctiva from the contralateral eye, in part with a conjunctival flap, and in part with lyophilised conjunctiva.

Except for some retraction of conjunctiva over the graft the postoperative course was uneventful, and he required no further ocular medication. Because the scleral spur had been removed, the anterior chamber

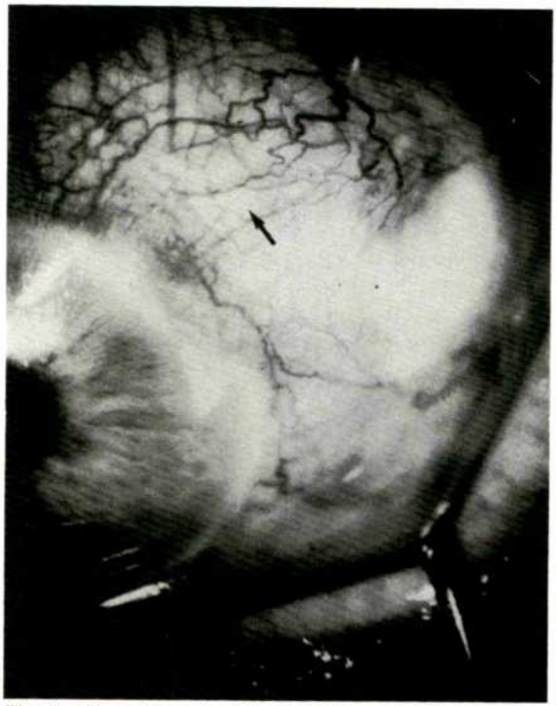

Fig. 1 *Necrotising sclerokeratitis. The sclera and overlying conjunctiva are necrotic but there is no surrounding severe inflammatory reaction. The cornea in the same area is infiltrated, with some peripheral corneal tissue loss. Anterior segment fluorescein angiography was performed in the area indicated (arrow).*

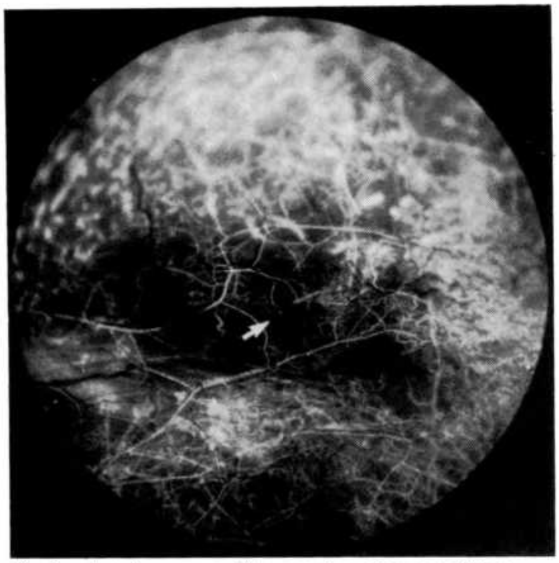

Fig. 2 *Anterior segment fluorescein angiogram of area shown in Fig. 1. In the late arterial phase the conjunctival and episcleral vessels in this area are not perfused. The large deep vessels which appear to contain blood have little or no flow in them. Early new vessel capillary loops are seen in the superficial tissue over the area of non-perfusion (arrow).*

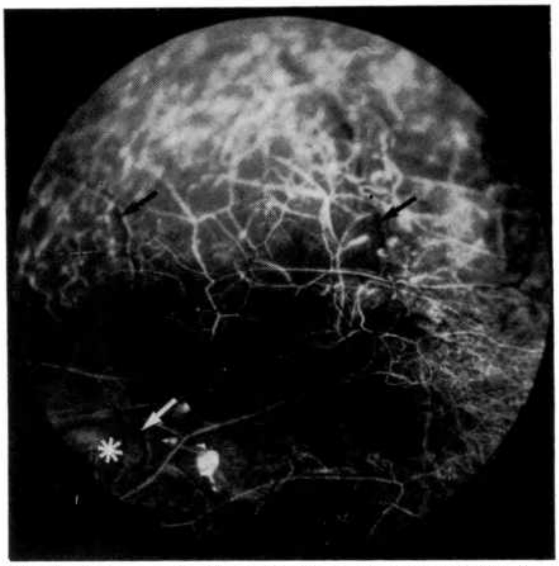

Fig. 3 *Later venous phase of same angiogram as in Fig. 2. The capillary network of the conjunctiva is fully perfused above, but both the conjunctival and episcleral vessels have failed to fill below, and this area remained non-perfused throughout the angiogram. The three large vessels (arrows) can be seen adjacent to the arrow in Fig. 1, but these vessels failed to fill with fluorescein even very late in the series. Some deep leakage is occurring below these vessels (asterisk).*

extended under the lamellar graft for several months (Fig. 4).

Six months later ulceration was noted at the lower end of the graft associated with an active scleritis. Fluorescein angiography subsequently confirmed the presence of vascular loops into the graft, which could be seen on the slit lamp, but also revealed another region of non-perfusion of deep vessels adjacent to the ulceration (see below). A second lamellar corneoscleral graft was performed on 30 June 1981, during which it was again found that the sclera underlying the area of non-perfusion was abnormal.

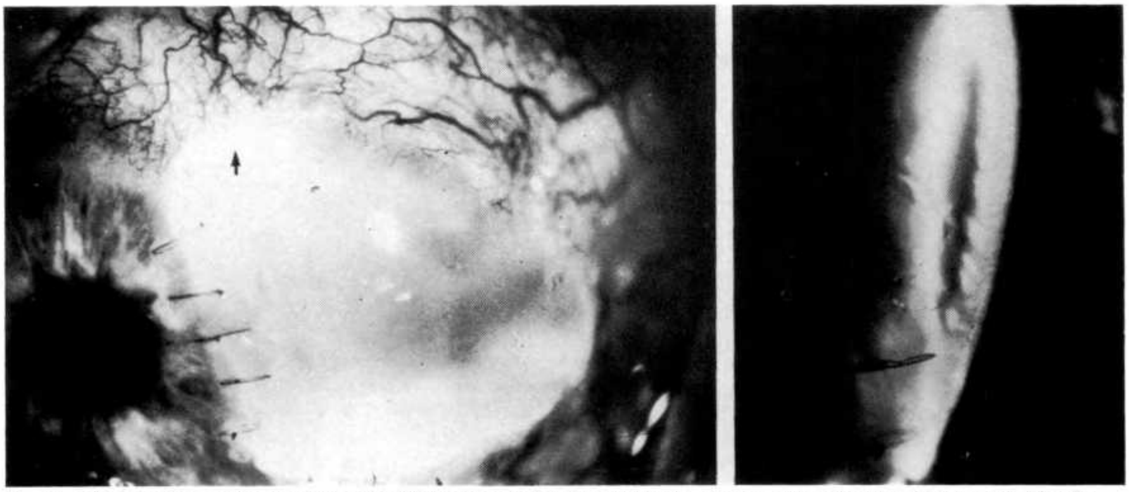

Fig. 4 *The appearance after the first graft. The histological material was obtained from the site indicated (arrow). The slit photograph shows the extension of the anterior chamber under the graft.*

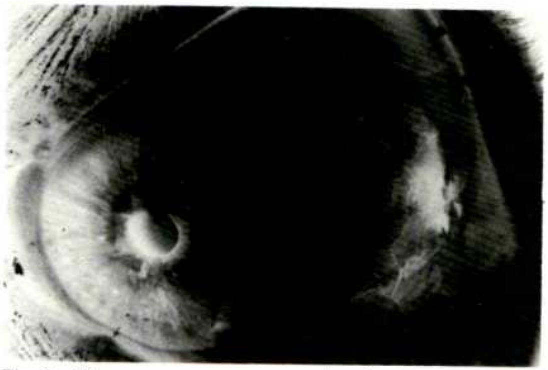

Fig. 5 *The appearance two years after the original episode. The grafted tissue has resorbed, leaving a transparent clear graft with absorption of the previously damaged sclera. This has been replaced by semitransparent scar tissue. The cornea has remained healed.*

Accordingly the excision was extended in order to replace this abnormal tissue. Three months later he had a myocardial infarction, and on admission to hospital he was found to have a small area of ulceration at the lower end of the second graft, which healed promptly with increased systemic steroid therapy.

Since then, although he has developed a cataract, the eye has remained quiet without inflammation. He has been maintained on 7·5 mg prednisolone to control his rheumatoid arthritis. The grafted cornea has remained clear, but the adjacent sclera has been gradually resorbed, leaving a thin transparent scar (Fig. 5).

ANTERIOR SEGMENT FLUORESCEIN ANGIOGRAPHY

Anterior segment fluorescein angiography was performed on 23 January 1981 (Figs. 2 and 3) at the site arrowed in Fig. 1 which was well away from the ulcerated area and adjacent to the edge of the infiltrated cornea.

Angiography revealed a rapid, normal conjunctival vascular filling but this had a well defined limit as the ulcer was approached. In the lower part of the angiogram both the conjunctival and episcleral vessels were either non-perfused or irregularly perfused. The major vessels, although clearly seen (Fig. 1) and presumably containing blood, did not show any fluorescence throughout the angiogram. The capillary loops in the hypoperfused cornea were irregular and abnormal, with evidence of new vessel formation indicative of chronic hypoxia. Deep leakage into the sclera was present underneath the episcleral vessels, arising from vessels in the region of the angle and ciliary body or from new vessels within the sclera.

Further anterior segment fluorescein angiography was performed at the lower end of the graft when the scleritis reactivated and the graft tissue began to ulcerate (20 June 1981). This showed active new vessel loops extending into both graft and normal cornea. There was also a large vascular tuft extending round the limbus below the graft. The vessels adjacent to the graft, however, were non-perfused (Fig. 6, arrow).

MICROSCOPY

No major accumulation of inflammatory cells com-

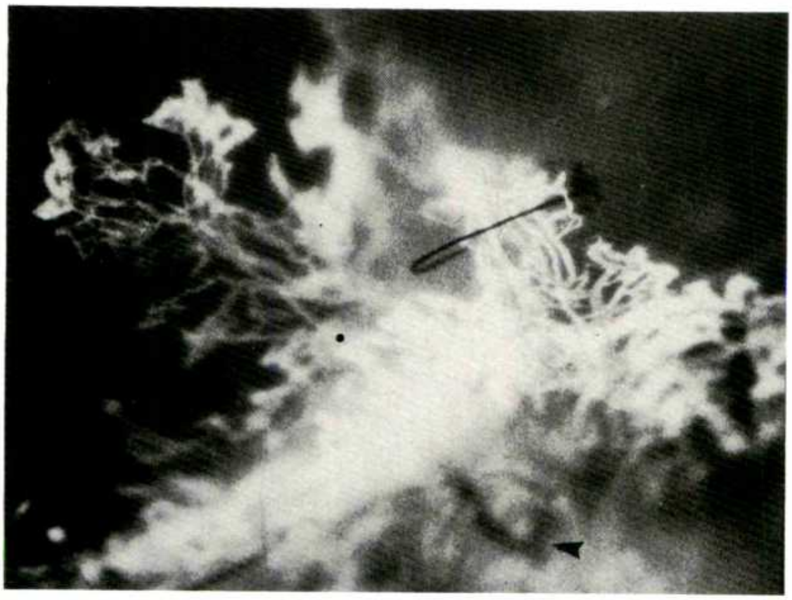

Fig. 6 *New vessel loops entering the graft at the site of the recurrence of the destructive process. The vessels below the graft are not perfused (arrowhead).*

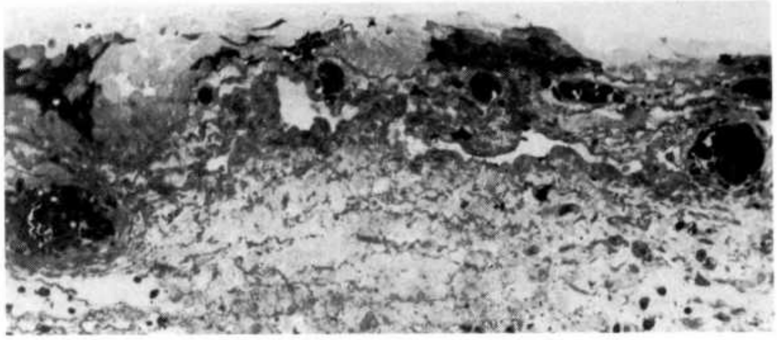

Fig. 7 *Patent vessels at the site of the angiogram, at the ulcer periphery. Although the vessels appear patent, the red blood cells are densely packed, suggesting sluggish or absent blood flow. There is no perivascular cellular infiltrate but obvious early destruction of collagen and adhesion of conjunctiva to the underlying tissue (×180).*

parable to that previously described at sites of scleral ulceration[4–6] was detected in the tissue removed from the area studied by angiography. Although compromised vascular function was known to be present (Figs. 1–3), examination of the blood vessels at this site (Fig. 7) revealed that, although the vessels appeared patent, red cells were densely packed, consistent with sluggish or absent flow. There was no perivascular cellular infiltrate associated with these vessels.

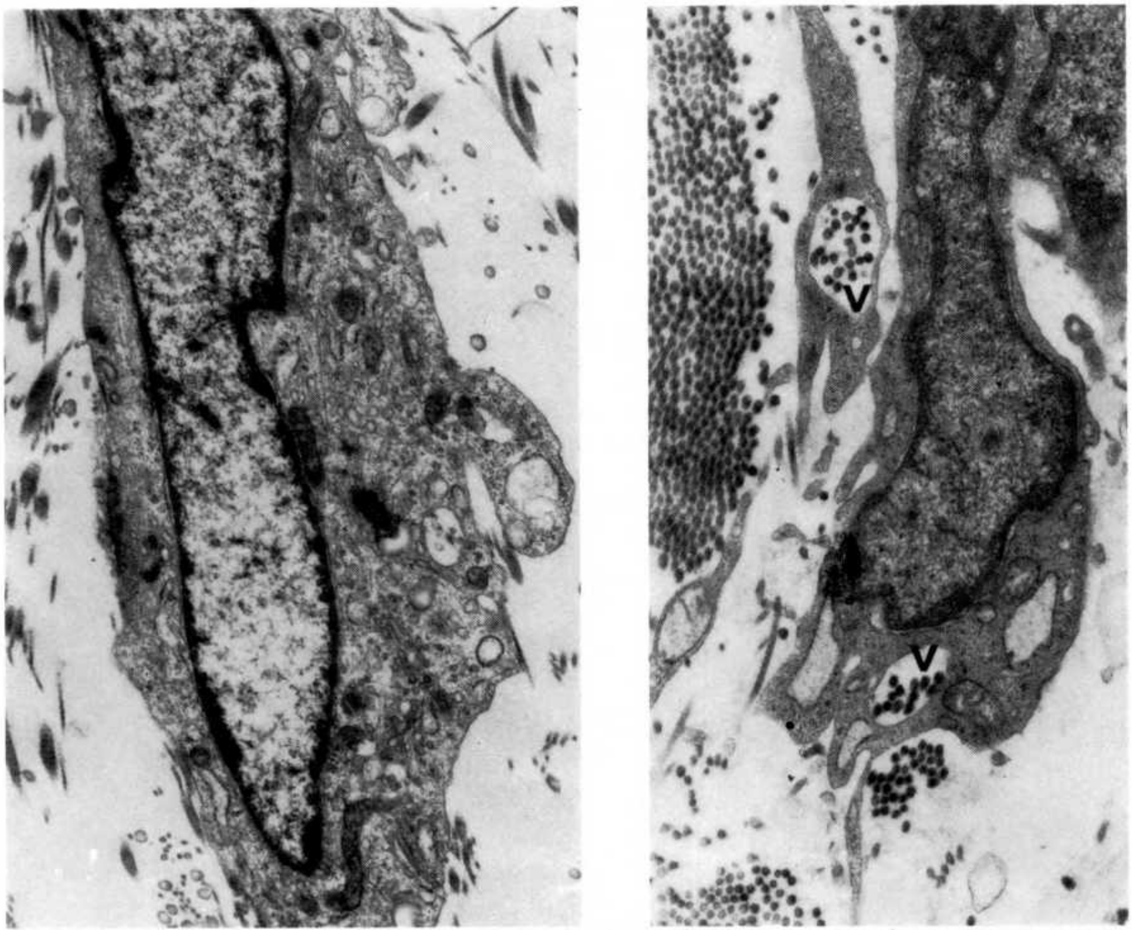

Fig. 8 *Electron micrographs of scleral stroma at periphery of frank ulcer. Left shows active fibroblastic cell (×15 375). Right shows collagen fibrils within intracellular vacuoles (*v*) in a fibroblastic cell (×15 375).*

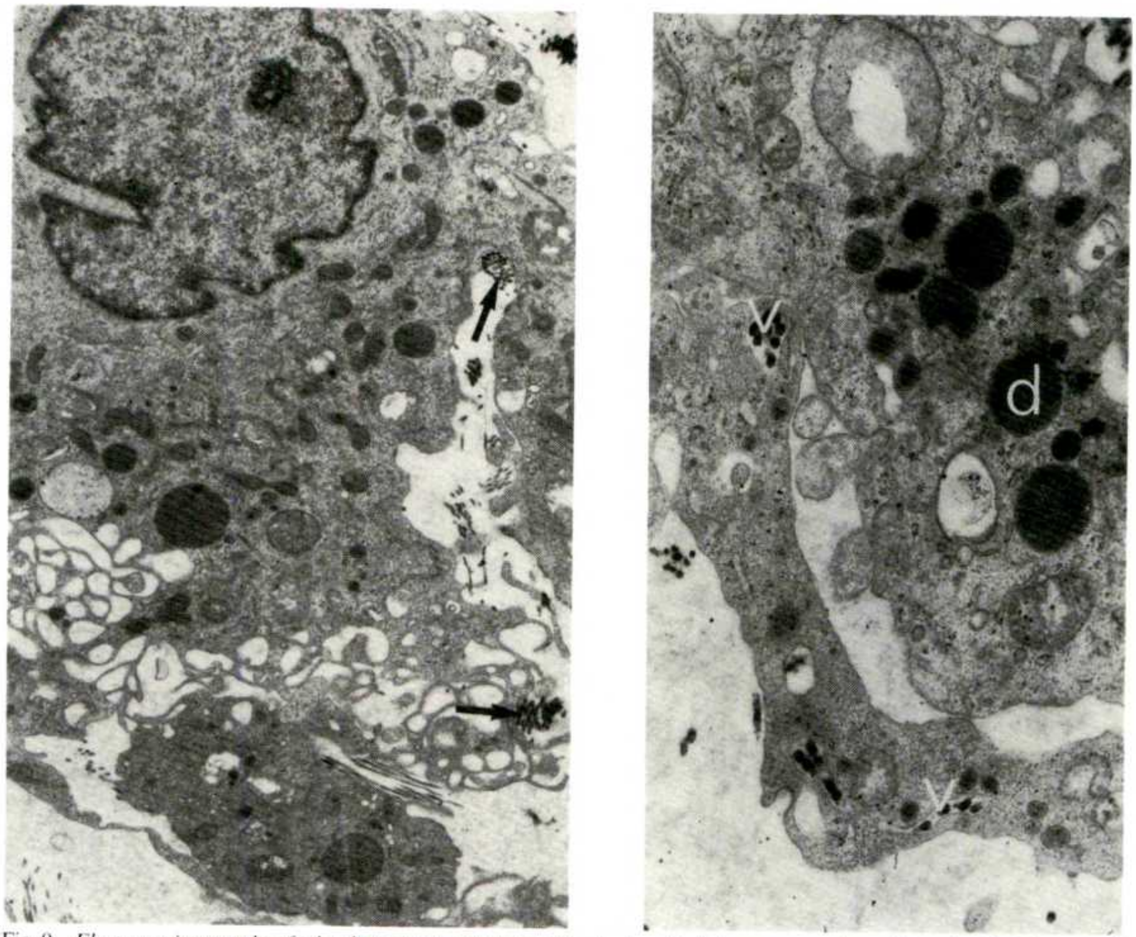

Fig. 9 *Electron micrographs of scleral stroma at periphery of frank ulcer. Left shows macrophage-like cell with elaborate cell surface in close contact with collagen fibrils (arrows) (×7145). Right shows collagen fibrils within vacuoles* (v) *in a macrophage-like cell which also contains numerous dense granules* (d) *(×15 655).*

The preliminary stages of matrix degradation in the conjunctiva and episclera were evident in this site, where there was no obvious demarcation between conjunctiva and episclera in the deeper tissues. The cellular element of the scleral connective tissue consisted of active-appearing fibroblastic cells and macrophage-like cells with elaborate cell surfaces and numerous cytoplasmic inclusions (Figs. 8 and 9, left). Both cell types were commonly observed with collagen fibrils or fibril fragments in close apposition with the cell membrane or pseudopodia, or partly or completely enclosed in membraneous folds and cytoplasmic vacuoles (Figs. 8 and 9, right). Dense cytoplasmic granules were frequently clustered within the macrophage-like cells in the vicinity of collagen fibril phagocytosis (Fig. 9, right).

In addition, degradative changes in collagen fibrils of the scleral matrix were apparently taking place without close apposition to active scleral cells. Collagen fibrils appeared to undergo swelling and unravelling (Fig. 10), which began at discrete sites and spread to involve extensive lengths of the fibril. In the outer sclera fibrils of large and small diameter appeared similarly affected.

No granulocytes or lymphocytes were found within these areas of matrix degradation.

Discussion

This is the first case in which the anterior segment angiographic appearances have been correlated with the pathological changes in necrotising scleral disease.

A constant angiographic feature of necrotising

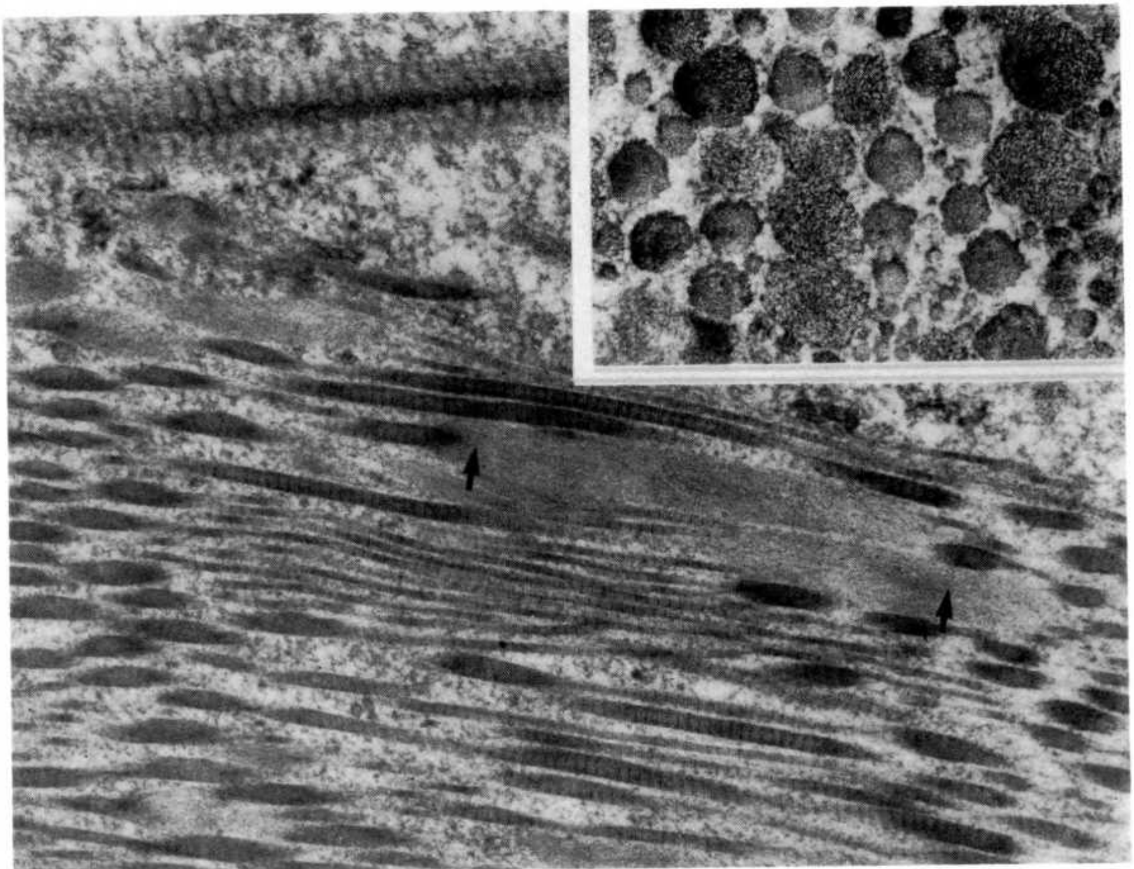

Fig. 10 *Electron micrographs of scleral stroma at ulcer periphery showing swelling and unravelling of collagen fibrils (arrows) in longitudinal (×29 270), and in transverse section (inset, ×44 000). Fibrils of all diameters are affected.*

scleritis, whether tissue loss occurs or not, is that the rapid circulation through dilated normal vessels, which is part of the normal inflammatory response, gives way to sluggish and finally total absence of flow in vessels in the region of the necrotising process. When the inflammation has been suppressed by treatment, a few of the vessels near the the periphery of the lesion may become reperfused, but in many no flow can be detected, suggesting that the vessels have been thrombosed.

Either these non-perfused areas remain without any apparent circulation from the superficial vasculature, being traversed by large anastomotic vessels, or new capillaries extend into them either as solitary budding vessels or in the form of a fan, leaving a functional capillary bed behind.

In the case reported here the diagnosis of necrotising scleritis was obvious, but the extent of the necrotising process was not clear. Anterior segment fluorescein angiography precisely localised the extent of the vaso-obliterative process in one direction. (To have detected the extent below would have required a further angiogram in this instance because of deep leakage of fluorescein). At operation, although the site of the angiography was a considerable distance from the obviously abnormal tissue, the conjunctiva was found to be adherent to the underlying episclera and the texture of the underlying sclera and adjacent cornea abnormally soft.

Following surgery the interpretation of fluorescein angiograms is more difficult. However, in this case, when a recrudescence of the scleritis occurred, postoperative fluorescein angiography was of considerable value both as an indicator of renewed inflammatory disease which warranted further surgery and as an aid in the placement of the second graft. On the basis of information obtained from the angiogram the excision was extended into tissue peripheral to the new ulceration, which, while superficially of normal appearance, was shown by electron microscopy to be already involved in the degradative process. In view of the fact that a further inflammatory episode followed the second graft (which was readily treatable with short-term steroid) it is probable that the excision was not quite extensive enough.

Electron microscopy of tissue excised from sites of vascular closure peripheral to the scleral ulcer showed that, in contrast to the ulcer centre[4,6] perivascular inflammatory cells were absent. However, on morphological criteria scleral stromal cells deep to these sites appeared highly active. Fibroblastic transformation of scleral cells throughout the full thickness of the stroma was associated with degradative changes in the matrix, often where the connective tissue appeared initially to be intact. Electron microscopy has shown[7] that in necrotising scleritis, as in other normal and pathological tissues[8-10] where rapid resorption of connective tissue is evident, collagen degradation may take place via two routes: active engulfment of fibrillar material by phagocytic cells, which then degrade the protein via the lysosomal pathway, and by an extracellular mechanism, possibly involving release or activation in the matrix of collagenolytic enzymes from active fibroblasts.

This study indicates that scleral destruction in necrotising scleritis is already in progress at sites of vascular closure, which can be demonstrated by anterior segment fluorescein angiography, quite distant to the major granulomatous infiltration which occurs in this disease. As has been demonstrated here, if surgery has to be performed on these patients, the dissection must be extended into areas where the vascular pattern is normal.

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Family studies in glaucoma*

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SUMMARY Two groups of patients with a family history of chronic open-angle glaucoma were compared with a normal population of 5919 individuals studied during the Bedford Glaucoma Survey. The mean screening intraocular pressure was significantly raised in both groups with a family history of chronic open-angle glaucoma. The prevalence rate of a raised intraocular pressure was 3·81 times that found in the normal population. This relationship was maintained when age-dependent prevalence rates were evaluated. No correlation between raised intraocular pressure and type of familial involvement could be determined. A 10- to 12-year follow-up of one group with a family history for open-angle glaucoma (101 patients) showed that 3% developed confirmed glaucoma, while an additional 5·9% were diagnosed as suspected chronic open-angle glaucoma. A letter survey of this group showed that 9 out of 63 respondents knew of additional family members who developed glaucoma over this 10–12-year period.

A well recognised risk factor in the development of chronic open-angle glaucoma is the presence of a family member with established disease. Perkins has demonstrated that, when family members of known cases of chronic open-angle glaucoma were evaluated, 11 new cases were found in 190 children and siblings of patients with the disorder.[1] In longitudinal studies in which first-degree relatives of patients with chronic open-angle glaucoma were followed up for 9–10 years a significant number had either developed chronic open-angle glaucoma or were highly suspect of having the disorder.[2 3]

It is the purpose of this paper to estimate by means of epidemiological methods the magnitude of the risk of developing a raised intraocular pressure as well as that of developing the disorder if one has a family member with the disease.

Materials and methods

Two populations of patients with a family history of glaucoma were evaluated (designated study populations). One group came from the Bedford Survey[4] (Bedford study population) and consisted of 101 persons from 90 families collected during the two years the Bedford Survey was undertaken (1965-7), who provided the information that a family member had a history compatible with chronic open-angle glaucoma. The second group consisted of patients studied at the Institute of Ophthalmology in 1970-3 and previously reported on by Perkins[1] (Institute study population) and consisted of 167 patients from 90 families who were relatives of patients under the care of one of the authors (ESP) for confirmed chronic open-angle glaucoma. In both study populations the patients' records were evaluated retrospectively.

The general population to which each of the above populations were compared were the individuals reported upon in the Bedford Survey and included 5919 out of the 5941 persons screened (designated normal population).[4] The 22 individuals excluded were those with ocular disease in which the IOP was altered by the ocular pathology. The data from the normal population obtained from the Bedford Survey of 1965–7 were also analysed retrospectively. Table 1 displays the age and sex distribution of the normal population. All subjects included in this study were over the age of 30 years.

The screening IOP refers to that pressure obtained on the initial evaluation.

A 10–12-year follow-up study of the Bedford study population was undertaken to investigate how many individuals developed glaucoma over this time period.

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Table 1 *Normal population: Bedford glaucoma survey: 5919 persons*

Age (years)	*Female* %	*Male* %
20–	0·05	0·05
30–	0·35	0·06
40–	18·14	14·50
50–	19·55	13·55
60–	14·87	7·66
70–	6·03	3·46
80+	0·76	0·37
Total	59·75	40·25

All individuals whose IOP was greater than 21 mmHg and who had no cupping or visual field loss were followed yearly from 1965 to 1977, and the data were obtained from the records of these visits. In addition a mail survey was undertaken in 1977 to determine if any additional members of the family had developed chronic open-angle glaucoma.

Results

Mean screening intraocular pressure. The mean screening IOP of the two study populations was significantly higher ($p<0·05$) than that in the normal population. Table 2 shows a comparison of the mean RE and LE IOP±SE in the three groups. Note that the mean values for both the study populations were comparable.

Prevalence of IOP greater than 21 mmHg. The prevalence of an increased IOP was three times greater in both study populations than in the normal population. In the normal population 508/5919 or 8·58% (SE=0·36) of individuals screened had a screening IOP greater than 21 mmHg. In contrast, 27/101 or 28·71% (SE=4·50) of individuals from the Bedford study population and 44/167 or 26·35% (SE=3·41) of individuals from the Institute study population had a raised intraocular pressure on initial testing.

Indirect standardisation for age and sex with respect to prevalence of increased IOP provides the standard mortality ratio (observed/expected) for both study populations with respect to sex (Table 3).

Table 2 *Screening intraocular pressure*

	Normal population	*Bedford study population*	*Institute study population*
OD Mean	16·45	18·03	18·08
SE	0·043	0·35	0·46
	5914	101	167
OS Mean	16·11	17·82	17·50
SE	0·042	0·35	0·39
	5909	101	167

Table 3 *Standardisation (indirect) for age and sex: standard mortality ratio (SMR) (observed/expected)*

	Bedford Study Population		*Institute Study Population*	
	SMR	*SE*	*SMR*	*SE*
Female	3·86	0·89	3·33	0·65
Male	3·23	1·02	5·36	1·26

Combining both study populations gives SMR=3·81; SE=0·45.

If one combines both study populations, the SMR= 3·81±0·45. This indicates that, if one has a positive family history for chronic open-angle glaucoma, there is a 3·81 times greater risk of having a screening IOP greater than 21 mmHg than in the general population. No statistically significant differences exist either between populations or within populations with respect to sex.

Fig. 1 displays the prevalence of an increased screening IOP with respect to age in the Bedford study population as compared with the normal population. Analysis of covariance shows that there

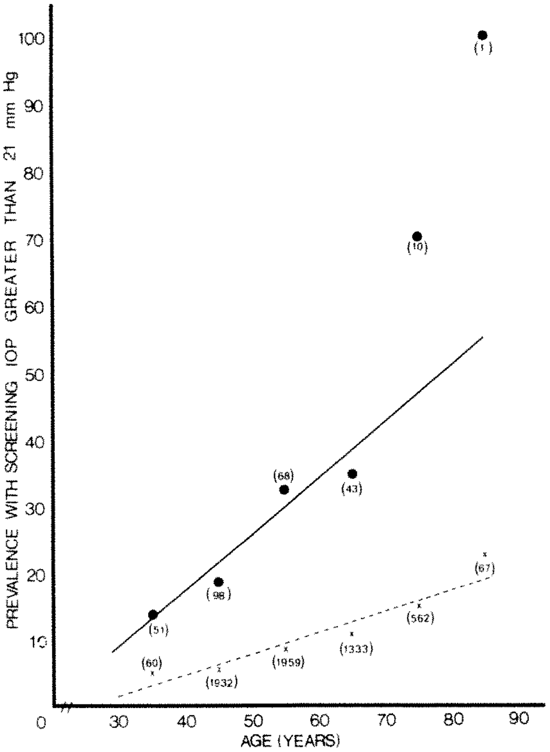

Fig. 1 *Prevalence of an increased screening intraocular pressure of greater than 21 mmHg with respect to age in a normal population and in a population of individuals who have a positive family history for chronic open-angle glaucoma. Parentheses indicate number of subjects in each age group.*

is a statistically significant difference between the slopes of the two curves ($p<0{\cdot}01$), indicating that the risk of having an increased IOP when there is a family history of chronic open-angle glaucoma exists throughout adult life.

Relationship of screening IOP greater than 21 mmHg to type of familial involvement in the Bedford study population. No correlation between elevated intraocular pressure and type of familial involvement could be determined. Fifteen of 69 or 21·7% of individuals who had at least one parent as the closest affected relative had an increased IOP. Five out of 17 or 29·4% of individuals who had at least one sibling as the closest affected relative had an increased IOP, and 5/15 or 33% who had as the closest affected relative a second-degree relative had an increased IOP.

Longitudinal follow-up study of Bedford study population. The 101 patients in the Bedford study population were followed up over a 10–12-year period. During this time 16 (15·8%) continued to carry a diagnosis of ocular hypertension, that is, an IOP consistently greater than 21 mmHg but no evidence of glaucomatous cupping of the optic nerve or visual field loss indicative of glaucoma. Six (5·9%) were started on antiglaucomatous therapy because of 'suspicious chronic open-angle glaucoma—that is, visual field and/or disc changes in the author's (ESP) opinion suggested early disease. An additional three (3%) developed visual field loss and/or optic nerve head cupping diagnostic of glaucomatous damage.

Mail survey of Bedford study population. The 101 patients from the Bedford study population were asked by mail if they knew of any additional members of their families who had developed chronic open-angle glaucoma. Of the 63 who responded 9 (14·3%) knew of other family members who had developed the disorder and were on treatment for it.

Discussion

This study confirms the fact that having a family history of chronic open-angle glaucoma puts a person at higher risk not only of developing the disease but also of having an abnormal increase of intraocular pressure. The fact that there is agreement between mean IOP and prevalence of raised IOP in two independent groups of patients with a positive family history provides confidence that the results are accurate in spite of the fact that neither of the groups was randomly chosen.

One of the major problems in a study relative to family history of chronic open-angle glaucoma is to determine whether patients in fact have a family history when they say they do. In the Institute group the positive family history was entirely accurate, as the individuals studied had family members under the care of one of the authors (ESP). In the Bedford Survey care was taken to ensure the accuracy of the family history, but in all cases one could not be sure it was entirely correct. Since the data from the two groups agree so well, we believe that the Bedford patients were moderately accurate with respect to their family history of chronic open-angle glaucoma.

The current study points out quite conclusively that, with aging, those individuals with a positive family history have an increasing chance of having an intraocular pressure greater than 21 mmHg. It also appears reasonable to assume that, with aging, the chance of developing suspected or frank glaucoma also increases, as it does in the general population. However, it is not inevitable that all patients with a positive family history who develop an increase in intraocular pressure actually develop glaucoma. A significant number studied had borderline IOPs for as long as four to five years without developing field loss and cupping. In fact the IOP of many of those studied returned to normal after several years of running in the low 20s. This observation has been reported previously in unselected patients with raised IOP.[5]

The individual with a family history of glaucoma who has a raised IOP must be followed up closely for the detection of changes related to the raised IOP. Older persons with a positive family history are probably at greater risk of developing glaucoma and should be watched more carefully. This hypothesis cannot be answered by this study, as the numbers of patients are too small and the follow-up period too short. Those factors which seem to have no role in the development of a raised pressure are sex and type of relative with raised pressure.

One can conclude from this investigation that the relative risk of having an increased IOP if a family member has chronic open-angle glaucoma is three to four times that in the general population. Furthermore, the percentage of patients who have a family history of chronic open-angle glaucoma who on long-term follow-up are found to develop either frank glaucoma or suspicious glaucoma is approximately 9%. This is almost 10 times the prevalence of glaucoma in the general population[6] and three times the incidence of glaucoma found by Perkins when he followed up for five to seven years the ocular hypertensives detected in the original Bedford Survey.[7] It is reasonable therefore to emphasise the importance of careful periodic ophthalmological examination of relatives of individuals who have chronic open-angle glaucoma.

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Effects of topical indomethacin pretreatment on argon laser trabeculoplasty: a randomised, double-masked study on black South Africans

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SUMMARY This randomised, double-masked study on 45 black South Africans compares the effect of topical indomethacin pretreatment with that of placebo on the immediate postoperative increase or reduction in intraocular pressure one week and one month after argon laser trabeculoplasty. There was no significant difference in the incidence and the magnitude of the immediate postoperative intraocular pressure increase between the two groups, though they occurred significantly later in the indomethacin-treated group ($p<0{\cdot}01$). Although no effect of indomethacin pretreatment on the intraocular pressure reduction was evident after one week, a significant adverse effect of the drug was demonstrated after one month ($p<0{\cdot}01$).

Since its introduction argon laser trabeculoplasty[1] has proved very successful in the treatment of open angle glaucoma.[2-6] It is indicated for patients whose intraocular pressures are not controlled on the maximum tolerated medical therapy.

The early complications of the procedure are well known.[7,8] Two of these are of great concern. The first is immediate postoperative intraocular pressure increase, which can lead to rapid visual field loss. The second is postoperative intraocular inflammation, which can possibly contribute to the immediate postoperative intraocular pressure increase and affect the long-term control of the glaucoma. A number of techniques have been tried in an attempt to overcome these problems. It has been found that argon laser trabeculoplasty, when applied to only one half (180°), rather than the whole circumference (360°) of the trabecular meshwork, can decrease the magnitude, but not the incidence, of the immediate postoperative intraocular pressure increase.[9] Corticosteroid pretreatment on the other hand does not influence either the immediate postoperative intraocular pressure increase or the intraocular pressure two months later.[10]

We conducted a randomised double-masked study using 1% indomethacin in aqueous suspension prior to argon laser trabeculoplasty to check the influence of this drug on the incidence and the magnitude of the immediate postoperative intraocular pressure increase as well as the intraocular pressure one week and one month after the operation. To our knowledge this is the first study to analyse the effect of topical indomethacin pretreatment on the intraocular pressures following argon laser trabeculoplasty.

Subjects and methods

Forty-five consecutive South African black patients for whom argon laser trabeculoplasty was indicated were included in this randomised, double-masked study conducted from August 1983 to May 1984. The study was approved by the Ethics Committee of Baragwanath Hospital, Soweto, South Africa, and all patients gave their formal consent. Each patient received treatment in one eye only. All had open-angle glaucoma, with intraocular pressures inadequately controlled by the maximum tolerated medication. The following patients were excluded from the study: those with only one eye; those under the age of 40, those who within the previous four months had undergone intraocular surgery in the eye to be treated; those in whom there was poor visibility of the trabecular meshwork due to an extremely narrow angle, corneal oedema, etc.; those with anterior uveitis; those who had previously received argon

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laser trabeculoplasty to one half of the angle in the eye to be treated; and those who were unable to co-operate at the slit lamp.

Two sets of identical bottles, one containing 5 ml of 1% indomethacin ophthalmic suspension in aqueous solution and one containing 5 ml of placebo, were supplied by MSD (Merck Sharp and Dohme International, South Africa). These bottles had previously been randomised and then labelled with consecutive numbers, in which sequence they were given to consecutive patients. The code was kept by one of us (MW), who was not directly involved in the study. One drop of indomethacin ophthalmic suspension (or placebo) was administered by a nursing sister to the eye to be treated at 2 hours, 1·5 hours, 1 hour, and 0·5 hour prior to the operation.

Argon laser trabeculoplasty was performed by one of us (YAG) between 9 am and 10.30 am, using the following technique. The eye to be treated was anaesthetised with one drop of 0·4% oxybuprocaine (Novesin). A three-mirrored Goldmann gonioscopy lens was placed on the eye. Fifty equally spaced burns over 180° were applied to the anterior part of the trabecular meshwork. The following laser setting was used: 800 mW for a duration of 0·1 second and a spot size of 50 μm.

The intraocular pressures of both the treated and untreated eyes were determined with a Goldmann applanation tonometer by one of us (YAG) at the following times: one hour preoperation; every hour postoperation for five hours (i.e., the immediate postoperative period); one week and one month postoperation (i.e., the early postoperative period). All preoperative glaucoma medications were continued during the postoperative period, but no additional medications (e.g., topical steroids or indomethacin) were given.

Corrected intraocular pressure changes were calculated for all times by subtracting the change in the intraocular pressure of the untreated eye from that of the treated eye. For the immediate postoperative period the maximum corrected increase in the postoperative intraocular pressure, as well as the hour at which it occurred, was noted. The intraocular pressures for each eye in the early postoperative period and before treatment of the same eye were compared. Pressure change of the untreated eye was then subtracted from the intraocular pressure change of the treated eye. By this method, which uses the untreated eyes as controls, one can eliminate bias caused by diurnal intraocular pressure variations, random fluctuations, and the patient's compliance with medical treatment.[9] Patients for whom data were not available after one week (one patient in the indomethacin-treated group, two in the placebo-treated group) and one month (three patients in the indomethacin-treated group, five in the placebo-treated group) did not return for follow-up.

Table 1 *Summary of patients' data*

Patients' data	*Indomethacin group*	*Placebo group*
Number of patients	23	22
Number of males	19	15
Number of females	4	7
Mean age	61·9±9·5 yr	57·0±9·5 yr
Preoperative mean intraocular pressure of the eyes to be treated	23·56±4·29 mmHg	23·72±5·68 mmHg
Preoperative mean corrected intraocular pressure[*]	4·52±6·06 mmHg	4·18±7·47 mmHg
Types of glaucoma:		
Primary open-angle	16 patients	19 patients
Pseudoexfoliation	5 patients	1 patient
Aphakic	1 patient	0 patients
Angle recession	1 patient	2 patients

[*] This value was calculated by subtracting the intraocular pressure of the untreated eye from that of the eye to be treated.

Patients' data are summarised in Table 1. There were 23 patients in the indomethacin-treated group (19 males, 4 females) with an average age of 61·9±9·5 years. In the placebo-treated group there were 22 patients (15 males, 7 females) with an average age of 57·0±9·5 years. Each patient received treatment in one eye only. Student's *t* test was used for all statistical comparisons between the two groups.

Prior to treatment the mean intraocular pressure of the eyes to be treated was 23·56±4·29 mmHg in the indomethacin-treated group and 23·72±5·68 mmHg in the placebo-treated group, there being no statistically significant difference between the two. Furthermore, there was no statistically significant difference between the mean corrected intraocular pressures of these two groups preoperatively; they were 4·52±6·06 mmHg in the indomethacin-treated group and 4·18±7·47 mmHg in the placebo-treated group.

Results

Table 2 summarises the maximum corrected intraocular pressure change during the first five hours for the indomethacin-treated group and the placebo-treated group. It also shows the hour at which this occurred. The mean maximum corrected intraocular pressure increase of the indomethacin-treated group was 1·39±4·18 mmHg and that of the placebo-treated group 1·63±5·8 mmHg. There was no statistically significant difference between the two groups. Furthermore, there was found to be no difference in the incidence of the intraocular pressure elevation between the two groups. In both groups 13 patients had raised intraocular pressures, two showed no

Table 2 *Maximum corrected intraocular pressure change during the first five hours after operation, and the hour at which it occurred*

Indomethacin group			*Placebo group*		
Patient no	*Corrected pressure change (mmHg)*	*Hour*	*Patient no.*	*Corrected pressure change (mmHg)*	*Hour*
1	+2	5	2	−1	1
3	−1	5	4	−3	1
7	+4	3	5	+3	2
8	+1	1	6	−3	1
10	+9	3	9	−6	4
11	+5	2	12	+1	1
15	+1	1	13	0	4
16	+4	1	14	+5	3
18	0	1	17	−5	1
20	+2	1	19	+2	1
22	−3	1	21	+10	1
24	−4	3	23	+3	1
25	−5	3	26	+12	1
27	+4	2	28	+4	1
29	+2	2	30	0	1
32	−1	2	31	+8	2
35	0	2	33	+1	1
36	+8	4	34	+6	2
37	−2	1	39	+3	2
38	+1	4	40	−13	1
43	−4	1	41	+10	1
44	−2	3	42	−1	1
45	+11	3			

Table 3 *Corrected intraocular pressure changes after one week and one month*

Indomethacin group (mmHg)			*Placebo group (mmHg)*		
Patient no	*One week*	*One month*	*Patient no*	*One week*	*One month*
1	−2	−4	2	−6	−11
3	−2	−1	4	–	–
7	−5	−5	5	−4	−5
8	−2	+2	6	−10	−5
10	0	−2	9	–	–
11	+1	−7	12	−4	−2
15	−3	−7	13	−4	−6
16	+3	−3	14	−1	−5
18	0	0	17	−8	−8
20	−8	−8	19	−4	−4
22	−10	−4	21	−10	–
24	−10	−8	23	−2	−8
25	−7	−8	26	−6	−4
27	−2	0	28	−2	−4
29	–	−5	30	−5	−3
32	−3	–	31	+2	−6
35	−5	−7	33	+1	−7
36	−4	+4	34	−5	−4
37	−5	−1	39	0	−6
38	−15	–	40	−10	–
43	−12	−8	41	−3	–
44	−8	–	42	−4	−7
45	+7	−1			

change, while eight patients in the indomethacin-treated group and seven in the placebo-treated group showed decreased intraocular pressures. On the other hand a statistically significant difference was found between the average times at which the maximum increase in the intraocular pressures occurred. In the indomethacin-treated group the average time for the maximum intraocular pressure increase was $2\cdot34\pm1\cdot30$ hours and in the placebo-treated group $1\cdot54\pm0\cdot96$ hours ($p<0\cdot01$).

Table 3 shows the corrected changes in the intraocular pressures after one week and one month for the indomethacin-treated group and the placebo-treated group. After one week the mean corrected intraocular pressure of the indomethacin-treated group was $-4\cdot18\pm5\cdot09$ mmHg, and that of the placebo-treated group $-4\cdot25\pm3\cdot46$ mmHg. This difference is not statistically significant. After one month, however, the mean corrected intraocular pressure of the indomethacin-treated group was $-3\cdot65\pm3\cdot66$ mmHg and of the placebo-treated group $-5\cdot59\pm2\cdot18$ mmHg. This difference is statistically significant ($p<0\cdot01$).

Discussion

The basis for the immediate postoperative intraocular pressure increase, which is often seen after argon laser trabeculoplasty, is not known, nor are the factors which contribute to the failure of the procedure. However, electron microscopic studies of preparations of the trabecular meshwork which were obtained immediately after argon laser trabeculoplasty showed shrinkage of the collagen fibres of the trabecular beams, accompanied by oedema and inflammation.[11] It is possible, therefore, that both inflammation (even if subclinical) and mechanical factors contribute to the immediate increase in the intraocular pressure following the operation. The presence of inflammation is not surprising in view of the fact that the burns are applied very close to the ciliary body and the iris root, which are one of the main sources of prostaglandin production in the eye.[12] The application of argon laser burns to the iris has long been known to be a cause of prostaglandin-mediated breakdown of the blood-aqueous barrier, which can be blocked partially by pretreatment with indomethacin.[12,13] Indomethacin is known to inhibit the synthesis of prostaglandins, but the drug cannot antagonise their effects once they have been formed.[14] It seems logical, therefore, to treat preoperatively with indomethacin so that the intraocular concentration of the drug will reach peak levels at the time of the operation, when synthesis of prostaglandins is likely to occur.

In our study we applied topical indomethacin at half-hourly intervals, starting from two hours prior to the operation. This method of application is very similar to that used in the pioneering studies in Japan,[15,16] in which topical indomethacin pretreatment was shown to suppress postoperative inflammation following cataract surgery in human eyes. In our study, however, we doubled the concentration of indomethacin, and used 1% rather than 0·5%. We are not aware of any studies which measure the penetration of topical indomethacin ophthalmic suspension in the human eye. In rabbits, however,[17,18] the drug was found to penetrate the cornea quickly, with a peak concentration of one-thousandth the concentration applied. Its rate of elimination from the aqueous humour was approximately 20% per hour.[17] From the above it seems that the application of even only one drop of 1% indomethacin an hour prior to surgery will produce a peak concentration of 8-9 µg/ml. This is well within the range of effective inhibition of prostaglandin synthesis by microsomal fractions of the anterior uvea of rabbits.[19,20] In view of the lack of information pertaining to the human eye, we assume that 4 drops of 1% topical indomethacin applied at half-hourly intervals can effectively suppress prostaglandin production following argon laser trabeculoplasty. We avoided postoperative indomethacin treatment, since it has been found from in-vitro and in-vivo studies on experimental animals that indomethacin inhibits prostaglandin degradation enzymes and the transport mechanism responsible for the removal of prostaglandins from the eye.[21,22]

We would also like to emphasise the advantages of using corrected intraocular pressures[9] in the assessment of the efficiency of argon laser trabeculoplasty. As compared with the normal eye the glaucomatous eye, with its impaired outflow facility, is known to sustain greater diurnal intraocular pressure fluctuations in response to the diurnal variations in the secretory activity of the ciliary body.[23] A number of patterns in the diurnal fluctuation of the intraocular pressure of glaucomatous patients are recognised.[24] This can be a source of bias when measurements of the intraocular pressure are taken at different times of the day. This problem is of importance in our study, in which argon laser trabeculoplasty was performed in the early morning, to enable us to follow up the patients for five hours immediately following the operation. When the patients subsequently returned for follow-up one week and one month after the operation, their intraocular pressures were usually measured in the early afternoon. In order to eliminate the potential bias caused by diurnal variations, we calculated corrected intraocular pressures, comparing the intraocular pressure of the treated eye with that of the untreated eye.

A further reason for using corrected intraocular pressures is to overcome the bias caused by poor compliance of patients. The well known problem of poor compliance of glaucoma patients[25] is particularly severe in our patients. It is our feeling that many patients who fail to take medications adequately prior to argon laser trabeculoplasty start to comply for at least a short period after treatment. (This is due in part to their realisation of the severity of their condition and their knowledge that argon laser treatment is an alternative to surgery.) In these cases a reduction in intraocular pressure following argon laser trabeculoplasty may be due in part to better compliance with medication and not solely to the laser treatment. The use of corrected intraocular pressures can help to overcome this bias.

We wish to draw attention to the fact that in the present study the person who carried out the argon laser trabeculoplasty (YAG) also measured the intraocular pressures before and after treatment. This is acceptable and does not cause bias, because the aim of the study was not to evaluate the effect of argon laser trabeculoplasty as such but to evaluate the effect of indomethacin or placebo pretreatment on the pressure reduction following argon laser trabeculoplasty. Since this was a double-masked study, a second person (MW) kept the code, and a nursing sister applied the indomethacin or placebo prior to treatment. The person who treated the patients and measured their intraocular pressures (YAG), and the nursing sister who applied the drops, had no way of knowing how each patient was pretreated.

In this randomised, double-masked study we found no significant difference in either the incidence or the magnitude of the mean maximum corrected intraocular pressure increase between the indomethacin-treated group (1·39±4·18 mmHg) and the placebo-treated group (1·63±5·8 mmHg) in the immediate postoperative period. However, it took longer for this maximum intraocular pressure increase to develop in the indomethacin-treated group (2·34 ±1·30 hours) compared with the placebo-treated group (1·54±0·96 hours). These differences in time were found to be significant ($p<0·01$). The changes were detected at an earlier time compared with previous studies.[9,10] The delay of the indomethacin-treated group in attaining the maximum intraocular pressure increase may be due to partial suppression of the inflammation by the indomethacin, leading to a slower development of the intraocular pressure increase. After one week there was no significant difference between the mean corrected pressure values of the two groups, the indomethacin-treated group being −4·18±5·09 mmHg and the placebo-treated group −4·25±3·46 mmHg.

When calculated for one month, however, the corrected falls in mean intraocular pressure were found to be significantly greater for the placebo-treated group. The mean corrected intraocular pressure change for the indomethacin-treated group was $-3{\cdot}65\pm3{\cdot}66$ mmHg and that of the placebo-treated group $-5{\cdot}59\pm2{\cdot}18$ mmHg ($p<0{\cdot}01$).

The above results clearly demonstrate a significantly adverse effect of pretreatment with indomethacin ophthalmic suspension on the intraocular pressure reduction one month after the operation. We therefore conclude that indomethacin ophthalmic suspension should not be used as a pretreatment for argon laser trabeculoplasty.

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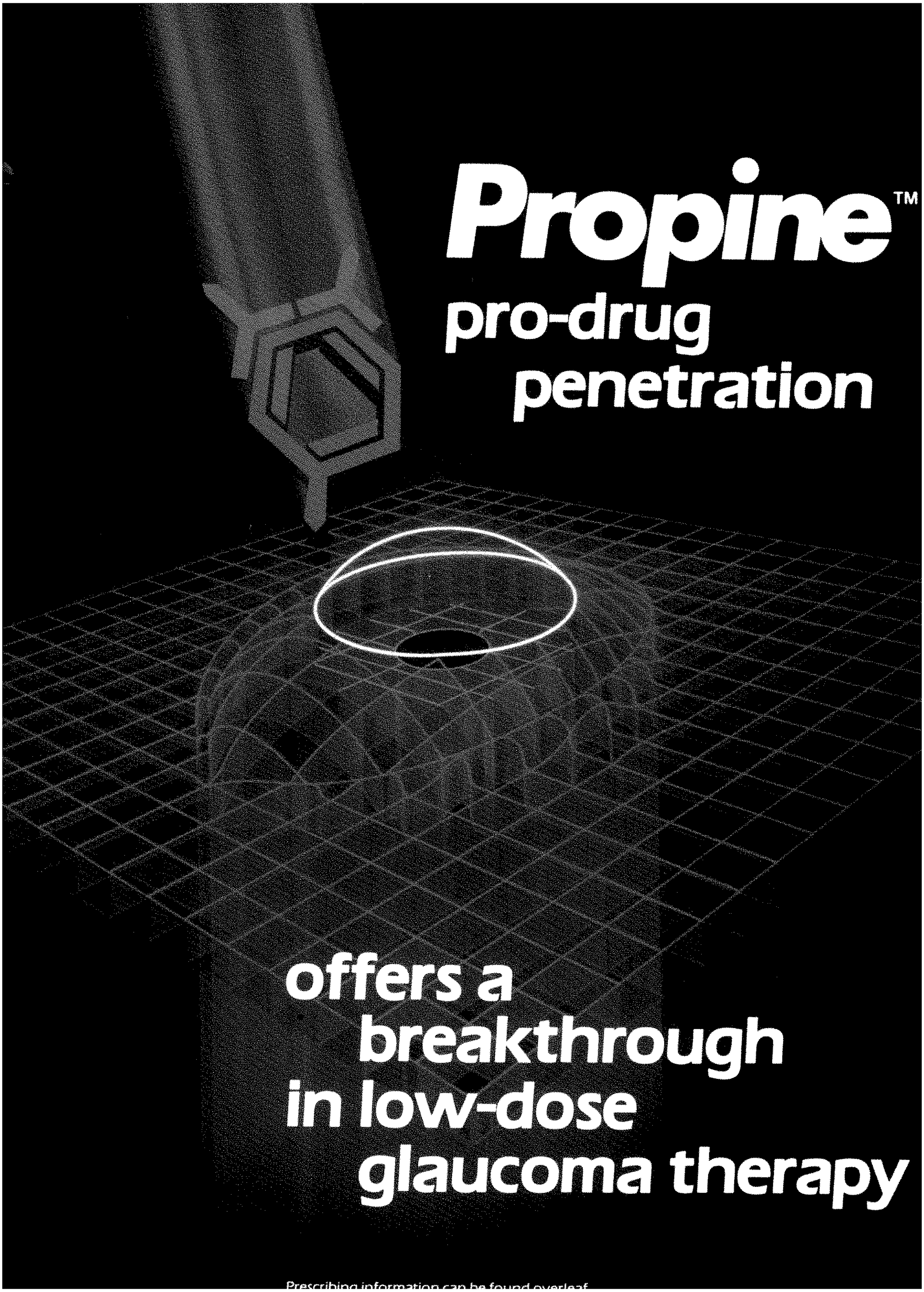

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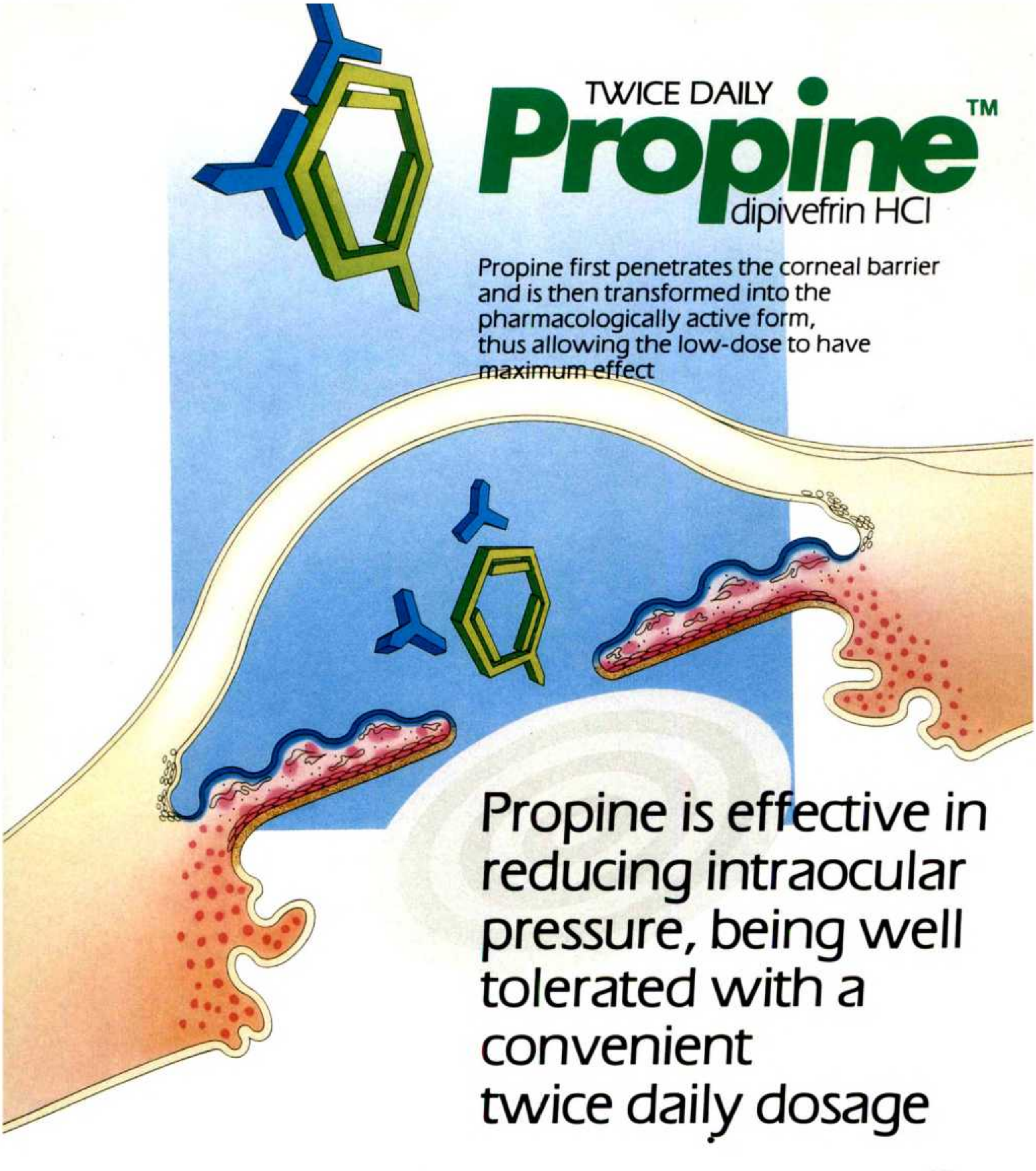

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Atracurium and intraocular pressure

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SUMMARY The effect of atracurium on intraocular pressure was studied by comparing it with pancuronium in a randomised controlled trial. The intraocular pressure was measured in patients undergoing cataract surgery before administration of the muscle relaxant, at 1, 3, and 5 minutes after its administration, and at 1 minute after tracheal intubation. Atracurium was found to decrease intraocular pressure to a significantly greater degree than pancuronium. The intraocular pressure after tracheal intubation was found to be significantly higher than that measured immediately after induction of anaesthesia. The authors conclude that atracurium provides an acceptable alternative to pancuronium for ophthalmic surgery but does not overcome the ocular hypertensive effect of tracheal intubation.

The increased use of general anaesthesia for intraocular surgery in recent years bears witness to the significant contribution which can be made by the anaesthetist to optimise conditions for surgery. Since most patients for such operations are elderly, a technique involving controlled ventilation of the lungs has the advantage of achieving optimal and stable intraoperative conditions at a lighter plane of anaesthesia with minimisation of postoperative side effects. The use of controlled ventilation for intraocular surgery is particularly advantageous, since intraocular pressure can be significantly lowered by inducing intraocular vasoconstriction with mechanical hyperventilation.[1 2] The non-depolarising neuromuscular blocking agents used to facilitate controlled ventilation have been shown to have no or minimal direct effects on intraocular pressure.

Atracurium is a new non-depolarising neuromuscular blocker whose effect on intraocular pressure has not heretofore been documented. In the present study the effect of atracurium on intraocular pressure was assessed and compared with that of pancuronium, a drug known to have no effect on intraocular pressure.[3 4]

Patients and methods

Patients giving informed consent and undergoing cataract extraction under general anaesthesia were included prospectively in the study. Premedication was with diazepam 10 mg 90 minutes prior to surgery.

Anaesthesia was induced with thiopentone, 4-5 mg kg^{-1} body weight intravenously, and followed one minute later by administration of the neuromuscular blocking agent. This consisted of atracurium 0·6 mg kg^{-1} or pancuronium 0·1 mg kg^{-1} body weight by random number sequence. As spontaneous breathing ceased, ventilation was controlled to maintain normocapnia (Siemens Elema 130 Infra Red CO_2 Monitor) with 70% nitrous oxide in oxygen via a face mask. Five minutes later orotracheal intubation was performed without prior spraying of the larynx with local anaesthetic, and thereafter ventilation was controlled mechanically and anaesthesia maintained with the addition of enflurane as required.

Measurements of intraocular pressure were made with a Digilab 30RT Pneuma-Tonometer/Tonographer, which was calibrated before, and rechecked after, each set of measurements. This instrument, designed exclusively for intraocular pressure measurement and using a pneumatic sensor, operates on the principle of applanation tonometry and records intraocular pressure continuously, in mmHg, with a freely moving pen recorder and a calibrated paper strip. Measurements were performed (by DFM or JBM) 1 minute after completion of thiopentone injection, 1, 3, and 5 minutes after the neuromuscular blocker was given, and 1 minute after intubation, in the eye not undergoing surgery. Values of intraocular pressure for both groups were compared by analysis of variance.

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Results

Ten patients were included in each group, demographic data on whom are outlined in Table 1.

Individual variation in intraocular pressure was marked, but the direction and degree of alteration in intraocular pressure in each group was similar. Mean values for intraocular pressure in both groups is shown on Table 2.

Intraocular pressure was found to be decreased 5 minutes after either muscle relaxant compared with postinduction values. Atracurium caused a greater fall in intraocular pressure than pancuronium at all times ($p<0·001$). Comparison of measurements taken at 1, 3, and 5 minutes after administration of either muscle relaxant failed to reach statistical significance ($0·05>p>0·025$), indicating that time was not a major contributor to the effect.

Comparison of values for both groups at 5 minutes after muscle relaxation with postintubation values indicated that a significant rise in intraocular pressure accompanied tracheal intubation in all cases ($p<0·01$).

Discussion

The goal of anaesthesia for intraocular surgery is to achieve steady state anaesthesia with a minimum of disturbance to the patient, so that the intraocular pressure does not rise to a level which would endanger the eye from forward prolapse of the intraocular contents once an incision is made. The achievement and maintenance of optimal operating conditions is particularly important if intraocular lens implantation is undertaken, a technique which is becoming so widespread as to be almost the rule in many centres. The fine manipulations required for lens implantation demand an immobile field, minimal bleeding, and a low intraocular pressure. A technique involving spontaneous ventilation by the patient may be used, since the intravenous and inhalational agents are known to lower the intraocular pressure[1-7] and so create a good operating field for surgery. The disadvantages of this technique include the need to use suxamethonium prior to intubation and the danger of carbon dioxide retention, both of which significantly increase intraocular pressure.[2,8] A further disadvantage is the need to attain deeper levels of anaesthesia, which, for the elderly population usually encountered, is undesirable. A technique using controlled hyperventilation can achieve similar operating conditions at a lighter plane of anaesthesia, and it eliminates the danger of straining during the critical stage of surgical incision. The anaesthetic induction agents, with the possible exception of ketamine,[9,10] lower intraocular pressure, and the non-depolarising neuromuscular blocking agents have no effect[4] or reduce intraocular pressure[3] so that this technique has much to recommend it for surgery.

Table 1 *Group characteristics of patients studied*

Patient group	*Sex M/F*	*Age (yr)*	*Weight (kg)*
Atracurium group	2/8	66·8±12·82 (SD)	58 0±11·1 (SD)
Pancuronium group	4/6	75·3±6·99 (SD)	62·2±15·0 (SD)

The development of newer and better neuromuscular blocking agents further promotes this technique. Atracurium, the drug assessed in the present study, has a rapid onset and short duration of action, with a lessened danger of prolonged action due to its unique property of spontaneous degradation at body temperature (Hoffman elimination).

In the present study atracurium decreased intraocular pressure to a statistically greater degree than pancuronium, though in a clinical setting this difference is unlikely to be obvious. All intraocular pressure measurements remained within the normal physiological range, and atracurium may therefore be considered an acceptable alternative to pancuronium for patients undergoing intraocular surgery.

At the given dosages conditions for intubation were found to be adequate for both groups. It is interesting to note, however, that the intraocular pressure rose significantly after the stress of laryngoscopy and intubation despite adequate neuromuscular blockade. Much has been written about the dangers of administering suxamethonium to patients with perforating eye injuries but little about the intraocular hypertensive effects of intubation. Clearly, if the effects of intubation cannot be attenuated, then much of the work in development of ultra-rapidly acting non-depolarising neuromuscular blocking agents will be in vain, at least in the field of emergency intraocular surgery. The authors consider that further attention must be focused on the cause

Table 2 *Intraocular pressure (mmHg±SD) for both patient groups at the stated measurement times*

Patient group	*1 min post-induction*	*Post muscle relaxant*			*1 min post-intubation*
		1 min	*3 min*	*5 min*	
Atracurium group	13·7±6 68	13·6±6·5	13 7±7·3	12·5±5 4	18·1±4·7
Pancuronium group	16·9±5·5	17·5±5·7	16·5±5·89	15·5±5·5	21·1±6·19

and elimination of the stress response to laryngoscopy and tracheal intubation.

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The ocular pulse and intraocular pressure as a screening test for carotid artery stenosis

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SUMMARY The ocular pulse and applanation tension were measured with a recording applanation tonometer in 38 patients suspected of having internal carotid artery stenosis. Abnormalities of the ocular pulse amplitude, intraocular pressure, or combinations of these two measurements were found in 23 (82%) of 28 patients who were subsequently found to have angiographic evidence of 50% or more stenosis of one or both internal carotid arteries. Of 10 patients without angiographic evidence of carotid stenosis the ocular pulse amplitude, intraocular pressure, or both were abnormal in five, but two patients had an ocular cause for abnormality and two of the remaining three had evidence of carotid disease in the form of atheromatous plaques. These results suggest that measurement of the amplitude of the ocular pulse in addition to the intraocular pressure can predict the presence of carotid artery stenosis and indicate the need for further investigation. If a tonometer capable of measuring the pulse amplitude was used routinely in ophthalmic examinations, it would provide a useful screening test for the early diagnosis and treatment of carotid artery disease and might thereby reduce the frequency of strokes.

Carotid artery disease is an important cause of strokes, and, if the condition could be recognised before symptoms arise, surgical treatment might be effective in reducing the incidence of death and disability from strokes. It is not surprising, therefore, that many non-invasive screening tests for carotid disease have been devised to detect patients requiring angiography. Such tests, however, are applied only when the patient presents with symptoms suggestive of vascular insufficiency.

Most people over the age of 40 require glasses for near work and are likely to attend an ophthalmologist or optometrist at regular intervals for a refraction, so that a screening test which was part of a routine ophthalmic examination could be applied on a large scale with little extra effort or cost. One such test is the measurement of the ocular pulse and the comparison of the pulse amplitude in the two eyes. Ophthalmologists and many optometrists routinely measure the intraocular pressure as a screening test for glaucoma, and some tonometers can indicate the ocular pulse amplitude, though the value of this measurement is rarely recognised, and only the mean level of pressure is normally recorded. As the amplitude of the ocular pulse reflects the volume of blood entering the eye with each cardiac pulse wave, it is dependent in part on the integrity of the arterial supply to the eye, and stenosis of the internal carotid would be expected to result in a reduced ocular pulse amplitude, and perhaps a low intraocular pressure.

The purpose of this paper is to compare the ocular pulse amplitudes and intraocular pressure with the results of carotid angiography in a series of patients suspected of having carotid artery disease.

Patients and methods

PATIENTS

The patients were derived from the Vascular Clinic of the Department of Ophthalmology and the Cardiovascular Department of the University of Iowa Hospitals and Clinics. They were suspected of having carotid artery disease and had had angiography of the internal carotid arteries (ICA). The ocular pulse studies were performed and the records analysed before the angiography results were known.

TONOMETRY AND OCULAR PULSE RECORDING

The ocular pulse amplitude was determined with a

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Goldmann applanation tonometer modified to give continuous recording of the intraocular pressure on a Hewlett-Packard heated stylus recorder. The Goldmann prism had a small chamber 2 mm in diameter drilled into the face of the prism, and the opening was covered with a very thin mylar membrane. The chamber was filled with water through lateral openings and connected by a short length of tubing to a pressure transducer. The fluorescein rings were adjusted in the normal manner and the prism centred so that the opening of the chamber lay within the applanated area. Under these conditions the intraocular pressure was transmitted through the cornea and the membrane to the fluid in the chamber and was recorded by the pressure transducer.[1]

CRITERIA OF ABNORMALITY OF THE OCULAR PULSE

The ocular pulse results from the influx of blood into the eye with each cardiac cycle, and the amplitude of the pulse wave (i.e., the change in intraocular pressure from diastole to systole) will depend on the pulse pressure and the adequacy of the blood supply to the eye, the volume of the choroidal vascular bed, and the relation between volume changes and pressure changes in the individual eye. In normal eyes the latter factor is probably the most important cause of interindividual variations. If a similar volume of blood enters the eye of normal subjects the resulting pressure change will be greater in small hypermetropic eyes than in large myopic eyes. A low pulse amplitude can therefore be due to myopia,[2 3] and the level below which the pulse amplitude is abnormal has to be modified with respect to the refraction.

Previous studies on a presumably normal population showed that a pulse amplitude of 1·5 mmHg or less occurred in only three out of 82 patients with hypermetropia or emmetropia, and only two out of 27 myopes had amplitudes of less than 1 mmHg. The difference in pulse amplitude between the two eyes exceeded 0·5 mmHg in only 2%.

The criteria of an abnormal pulse based upon the above findings were: (1) a pulse amplitude of 1·5 mmHg or less for hypermetropic and emmetropic eyes; (2) a pulse amplitude of 1·0 mmHg or less for myopic eyes (>−1·00 D); (3) a difference between the pulse amplitudes of the two eyes of more than 0·5 mmHg.

In the same normal population an intraocular pressure of 10 mmHg or less was found in only 7·3% and a difference in pressure between the two eyes of 3·0 mmHg occurred in only 2·75%.

The criteria chosen for considering the intraocular pressure abnormal were: (1) an applanation reading of 10 mmHg or less in one or both eyes; (2) a difference of 3·0 mmHg or more between the two eyes.

Results

Thirty-eight patients who subsequently underwent carotid angiography were examined, and the results can be summarised as follows.

CASES WITH ABNORMAL OCULAR PULSE AMPLITUDES (Table 1a)

There were 26 cases with a low ocular pulse amplitude and/or an intraocular difference in amplitude of more than 0·5 mmHg. Twenty-one of these cases (81%) were found to have angiographic evidence of internal carotid artery stenosis in one or both arteries. Of the five cases with abnormal pulses but no stenosis three had atheromatous plaques in the internal carotid artery, including one patient (case 3) who had had an occlusion of the central retinal artery and one patient with amaurosis fugax (case 27). It is possible, therefore, that there was reduced flow in the arteries in these patients, though no stenosis was reported on angiography.

The two remaining cases with abnormal pulses but no stenosis consisted of one patient who was subsequently diagnosed as having low-tension glaucoma (case 14) and one patient with amaurosis fugax (case 41). Abnormally low pulse amplitudes are known to occur in some patients with low-tension glaucoma,[4] and this may be the reason for the false positive results in this case. The remaining case with abnormal pulses but no stenosis gave a history of amaurosis fugax, which suggests an intermittent reduction of blood supply to the eye in spite of normal angiography.

CASES WITH NORMAL PULSE AMPLITUDE BUT ABNORMAL OCULAR TENSIONS (Table 1b)

There were two patients in this group who were both found to have stenosis of one or both ICAs.

CASES WITH NORMAL OCULAR PULSE AMPLITUDES AND NORMAL TENSIONS (Table 2)

There were 10 cases in this group and angiography showed no stenosis in five cases but stenosis in the other five. In three of the latter five there was a difference of 0·5 mmHg between the pulse amplitudes of the two eyes, but by the criteria used these must be included in the false negative rate of 50%.

The results in terms of positive and negative findings related to the angiographic reports are summarised in Table 3.

Discussion

Ophthalmodynamometry, ophthalmoplethysmography, photoplethysmography, and Doppler flow studies have all been used as non-invasive tests for carotid artery disease, and the results of different

Table 1a *Cases with abnormal ocular pulse amplitudes*

Case no.	*Mean pulse amplitude mmHg*	*Difference in amplitude mmHg*	*Tensions mmHg*	*Difference in tensions*	*Angiographic findings*	*Other findings*
3	OD 1·5 OS 1·5	0·0	OD 26 OS 17	9·0	Carotid plaques but no stenosis	OD central retinal artery occlusion, doppler abnormal
5	OD 0·5 OS 0·7	0·2	OD 18 OS 21	3·0	Total occlusion R ICA Almost total occlusion L ICA	
6	OD 0·25 OS 9·5	0·25	not recorded		Atheroma R ICA, no stenosis 75% stenosis L ICA	
7	OD <0·5 OS <0·5	0·0	OD 11 OS 11	0·0	Severe ulcerated plaques R ICA Total occlusion L ICA	
8	OD <0·5 OS 0·0	0·25	OD 9 OS 10	1·0	Complete occlusion both ICAs	
9	OD 0·5 OS 0·75	0·25	OD 11 OS 9	1·0	Severe stenosis both ICAs	
12	OD 2·25 OS 1·25	1·0	OD 10 OS 6	4·0	Total occlusion L ICA	
14	OD 0·75 OS 0·75	0·0	OD 15 OS 20	5·0	Minimal irregularity L ICA but no stenosis	History of amaurosis fugax; diagnosed low tension glaucoma
17	OD 0·75 OS 1·5	0·75	OD 28 OS 12	16·0	Complete occlusion R ICA 90% occlusion L ICA	Severe peripheral vascular disease, central retinal artery occlusion OD
18	OD 2·0 OS 0·75	1·25	OD 14 OS 20	6·0	Bilateral occlusion ICAs	
19	OD 0·5 OS 0·25	0·25	OD 16 OS 16	0·0	Minor irregularity R ICA Complete occlusion L ICA	Central retinal artery occlusion OS
20	OD 1·75 OS 1·25	0·25	OD 16 OS 16	0·0	Partial occlusion R ICA Complete occlusion L ICA	
21	OD 0·75 OS 0·75	0·0	OD 11 OS 8	3·0	Plaques R ICA Narrowing L common carotid and severe disease L ICA	
22	OD 0·75 OS 0·5	0·25	OD 13 OS 11	2·0	Plaques both ICAs but no stenosis	
25	OD 3·5 OS 2·0	1·5	OD 15 OS 13	2·0	Occlusion of L ICA	
26	OD 2·25 OS 1·25	1·0	OD 9 OS 9	0·0	Irregularity R bifurcation 95% stenosis L ICA	
27	OD 7·5 OS 6·0	1·5	OD 20 OS 19	1·0	Ulcerated plaque R carotid at junction Ulcerated plaques L ICA	Amaurosis fugax OS
30	OD 2·0 OS 4·0	2·0	OD 18 OS 22	4·0	90% occlusion R ICA 50% occlusion L ICA	
31	OD 3·0 OS 2·25	0·75	OD 12 OS 10	2·0	Total occlusion L ICA	
33	OD 6·5 OS 4·75	1·75	OD 20 OS 20	0·0	Minimal irregularity R ICA Tight stenosis origin L ICA	Hollenhorst plaques OS
34	OD 2·0 OS 3·0	1·0	OD 38 OS 22	16·0	Stenosis R ICA	Open-angle glaucoma
36	OD 1·5 OS 1·5	0·0	OD 9 OS 9	0·0	Less than 50% stenosis both ICAs	
37	OD 1·0 OS 1·0	0·0	OD 10 OS 10	0·0	No report R ICA 90% stenosis L ICA	
39	OD 4·0 OS 5·5	1·5	Not recorded		Plaque R common carotid. Total occlusion R ICA on repeat angiography	
41	OD 3·5 OS 4·5	1·0	OD 14 OS 14	0·0	No evidence R carotid disease	Amaurosis fugax OD
42	OD 5·0 OS 3·0	2·0	OD 18 OS 12	6·0	No report R Total occlusion L ICA	

Table 1b *Cases with normal pulse amplitudes but abnormal tensions*

Case no.	*Mean pulse amplitude mmHg*	*Difference in amplitude mmHg*	*Tensions mmHg*	*Difference in tensions*	*Angiographic findings*	*Other findings*
1	OD 2·5 OS 2·25	0·25	OD 7·0 OS 5·0	2·0	R ICA within normal L ICA occlusion	Venous stasis retinopathy OS
32	OD 3·5 OS 4·0	0·5	OD 12 OS 16	4·0	90% stenosis R ICA 100% stenosis L ICA	

tests have been reviewed by many authors.[5-7] All these methods require special apparatus and do not form part of a routine ophthalmic examination. They are all capable of correctly diagnosing carotid artery occlusion (particularly if it is unilateral) in a high percentage of cases.

The results of the present study suggest that abnormalities of the ocular pulse and intraocular pressure have a diagnostic value similar to that of other non-invasive tests. Eighty-two percent of cases were correctly diagnosed as having stenosis of one or both ICAs, and these results confirm and amplify previous studies on the ocular pulse.[8-10] False positive results were found in five out of 10 patients without angiographic evidence of stenosis of the internal carotid, but two patients had ocular disease to account for the abnormal ocular pulse and two of the remaining three patients had angiographic evidence of severe atheromatous disease of the ICA and could therefore be considered as true positive results. However, a further patient with atheromatous disease of the carotids had normal pulse amplitudes and applanation tensions.

The degree of stenosis of the ICA which is reflected in an abnormal ocular pulse cannot be assessed exactly from the present series, as the stenosis was not always quantified in the angiography report. All the patients described as having 75 to 100% occlusion were correctly diagnosed. In three patients with normal ocular pulses the angiographic findings were described as 'occlusion,' 'focal stenosis,' and '50 to 60% stenosis' respectively. It is probably necessary to have at least 50% stenosis to reduce the ocular pulse significantly, a figure which agrees with experimental findings.[11]

The criteria used for abnormality of the ocular pulse were a difference of more than 0·5 mmHg between the two eyes and/or a pulse amplitude less than 1·5 mmHg for hypermetropes and emmetropes, and 1·0 mmHg for myopes. A difference in pulse

Table 2 *Cases with normal ocular pulses and normal tension*

Case no.	*Mean pulse amplitude mmHg*	*Difference in amplitude mmHg*	*Tensions mmHg*	*Difference in tensions*	*Angiographic findings*	*Other findings*
2	OD 2·0 OS 2·25	0·25	OD 12 OS 12	0·0	Focal stenosis R ICA No stenosis L ICA	
4	OD 2·5 OS 2·5	0·0	OD 15 OS 15	0·0	Ulcerated plaques both ICAs; no stenosis	
10	OD 3·0 OS 3·0	0·0	OD 20 OS 20	0·0	50 to 60% stenosis R ICA	
13	OD 3·0 OS 3·0	0·0	OD 18 OS 18	0·0	Internal fold R ICA, no stenosis; plaques L ICA, no stenosis	
15	OD 3·0 OS 3·5	0·5	OD 15 OS 13	2·0	Plaques bifurcation and R ICA; extensive plaques L ICA	
23	OD 3·5 OS 3·0	0·5	OD 14 OS 14	0·0	Plaques both carotids but no stenosis	Cerebral infarcts
24	OD 2·0 OS 2·5	0·5	OD 14 OS 14	0·0	Total occlusion R ICA; atheroma carotid syphon L	
28	OD 4·5 OS 4·0	0·5	OD 18 OS 16	2·0	Stenotic area R ICA; significant stenosis L ICA	
29	OD 2·25 OS 2·0	0·25	OD 14 OS 14	0·0	No stenosis ICAs	Branch artery occlusion OS
40	OD 5·2 OS 4·7	0·5	OD 14 OS 14	0·0	Complete occlusion L ICA	

Table 3 *Summary of results in 38 patients*

	No. of cases	*Percent*
Carotid stenosis correctly diagnosed	23	82·14
False negatives	5	17·86
No stenosis correctly diagnosed	5	50·0
False positives	5*	50·0

*Two patients had ocular causes for abnormality.

amplitude of 0·5 mmHg is suggestive of carotid artery disease but was found in 14% of an apparently normal population,[2] and this criterion is likely to lead to more false positive results than an abnormally low amplitude.

In the absence of ocular disease or high myopia an ocular pulse amplitude less than 1·5 mmHg or a difference of more than 0·5 mmHg between the two eyes and/or applanation reading of 10 mmHg or less is an indication of carotid artery disease and warrants further investigation.

The importance of these findings is not simply that the ocular pulse provides another non-invasive test of carotid artery blood flow but that measurement of the ocular pulse could be applied with tonometry as a presymptomatic screening method during a routine ophthalmic examination in the same way as tonometry is used as a screening method for glaucoma. It does demand, however, that the tonometer used is capable of measuring the amplitude of the ocular pulse. Apart from the instrument used in this study (which is not in production), there is only one type of instrument specifically designed to provide a recording of the ocular pulse. The Applanation Pneumotonograph (Alcon Surgical) and the Model 30 R/T Pneuma-Tonometer Tonographer (Digilab) both have facilities for recording the ocular pulse. The latter manufacturer also produces an oculocerebrovasculometer which includes a suction cup, so that the ocular pulse can be measured at various intraocular pressures.[11] Any recording Schiøtz-type indentation tonometer can also be used to detect differences in pulse amplitudes between the two eyes, but the absolute value of pulse amplitude is more susceptible to errors induced by the weight of the instrument and the indentation of the plunger, which combine to raise the intraocular pressure of the eye being measured.

Applanation tonometry with the Goldmann prism is widely accepted as the standard of reference for tonometry and combines ease of use with high accuracy. Unfortunately it does not produce a recording of the pressure or ocular pulse, and the modification used in the present study was developed for this reason. It is possible to estimate the pulse amplitude by setting the semicircles of fluorescein so that they coincide first at their maximum excursion and then at their minimum excursion and noting the reading on the drum at each position. This method is less reliable than measurement from a recording, as the drum is calibrated in steps of 0·2 g (2 mmHg), so that small differences are difficult to measure accurately.

Carotid stenosis is a serious condition and is amenable to surgical treatment, so that it is a suitable candidate for presymptomatic detection if suitable screening methods were widely available. The measurement of the ocular pulse by tonometry would seem to offer a screening method easily applied during a routine ophthalmic examination. The ideal instrument for this would be an applanation tonometer with a recording system or an electrical output which could drive a small microprocessor with a visual display which could present the mean pressure and average a number of pulses to give a mean pulse amplitude.

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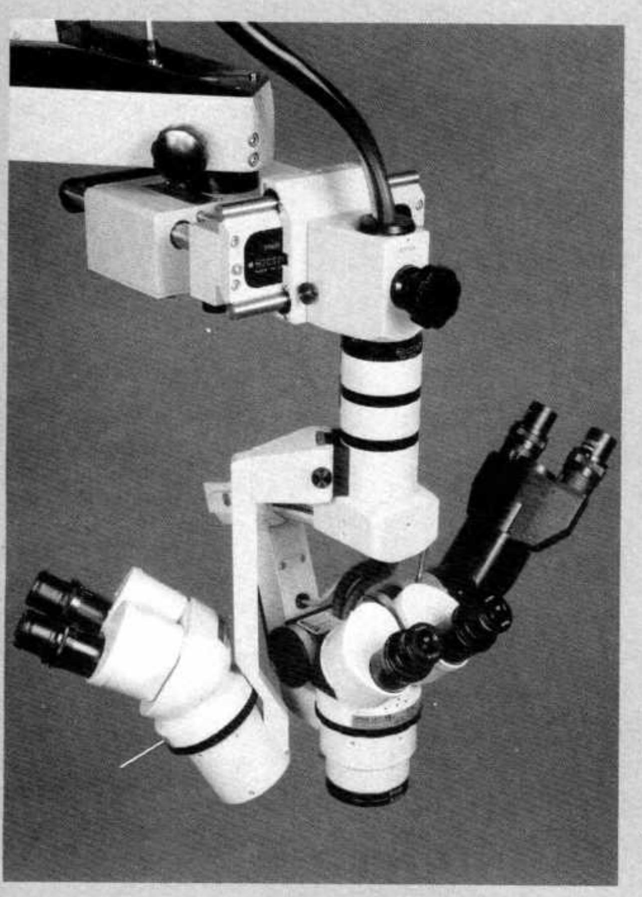

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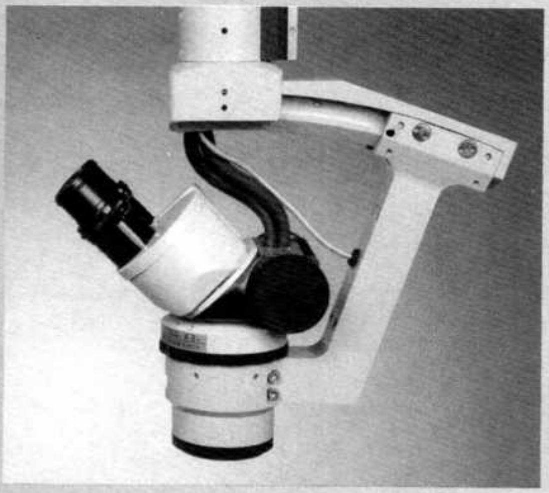

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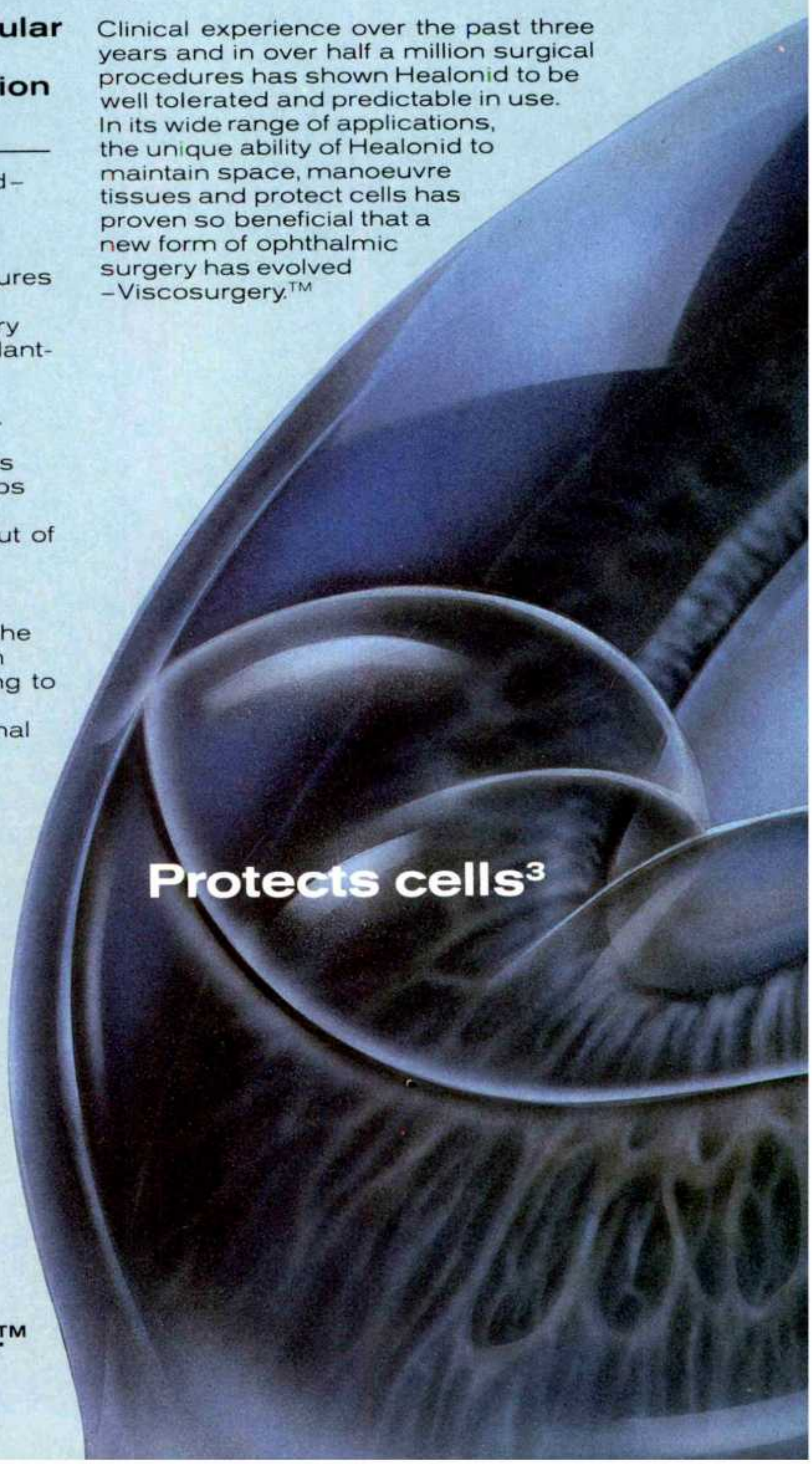

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Syndrome of ischaemic ocular inflammation: six cases and a review

N A JACOBS AND A E A RIDGWAY

From Manchester Royal Eye Hospital

SUMMARY Patients with carotid occlusive disease may develop a variety of symptoms and signs secondary to chronic ocular ischaemia. We report six cases affecting nine eyes and review the findings of teichopsia, anterior segment ischaemia, venous stasis retinopathy, and ocular neovascularisation. The assessment and surgical management of carotid obstruction are discussed. Some comments on the relevance of coexisting diabetes are made.

Although much attention has been paid to the acute ocular manifestations of carotid arterial disease, the chronic aspects have been less well reported. Retinal ischaemia is a more familiar concept than ischaemia of the eye as a whole.

The syndrome of ischaemic ocular inflammation described by Knox[1] consists of amaurosis fugax, pain without photophobia, and marked reduction in visual acuity disproportionate to the degree of inflammation. The pupil is dilated, and the fundus shows midperipheral haemorrhages and arterial narrowing.

We discuss the manifestations of chronic ocular ischaemia in six patients with underlying carotid occlusive disease. Successful management may depend on expeditious identification and referral of these patients.

Case reports

CASE 1

A woman aged 39, a smoker and a hypertensive with a history of right-sided transient ischaemic attacks and angina, presented with a two-year history of blurred left vision. This followed an episode of amaurosis fugax. She also complained of pain and persisting after-images in this eye for two months. Visual acuity (VA) was 6/12, with mild anterior chamber activity and early formation of peripheral anterior synechiae (PAS). The fundus showed marked venous stasis with beading, haemorrhages, and microaneurysms (Fig. 1). Fine disc new vessels were present.

We saw her one month after the successful saphenous by-pass graft for a left common carotid artery occlusion which had been demonstrated on angiography (Fig. 2).

CASE 2

A man aged 55, a smoker, presented with a five-day history of a 'fierce pain' over the right eye associated with blurred vision. VA was 6/36, with an unreactive dilated pupil, rubeosis of the angle, and an intraocular pressure (IOP) of 30 mmHg. Iris angiography confirmed ischaemia. There was also venous stasis retinopathy (Fig. 3) associated with cotton-wool spots. On review three months later episcleral injection, uveitis, and new vessels over the disc were also observed.

A left carotid bruit was heard. Angiography revealed occlusion of the right internal carotid artery and left internal carotid stenosis (Fig. 4). A left carotid endarterectomy was performed.

One year after the patient's initial presentation the right VA was perception of light (PL), with formation of a complicated cataract.

CASE 3

A man aged 67, a smoker and a hypertensive recovering from a right hemiparesis, presented with a six-month history of gradually deteriorating left vision. He also complained of pain over the left eye and a persisting after-image described as a 'jagged gold light'. His VA was counting fingers (CF), with episcleral injection, anterior chamber flare, early

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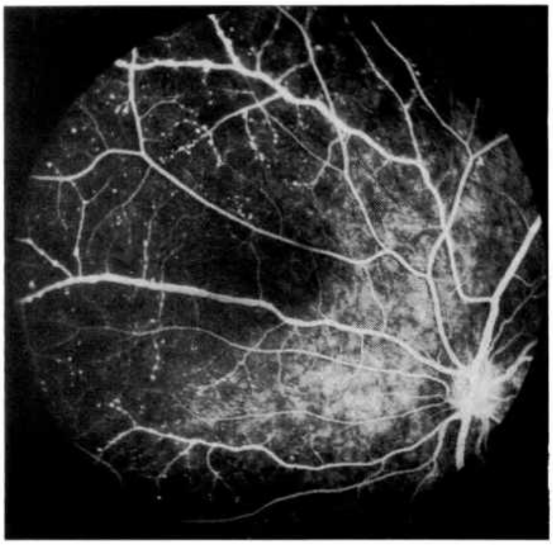

Fig. 1 *Left fundus fluorescein angiogram (case 1) showing microaneurysms and venous beading.*

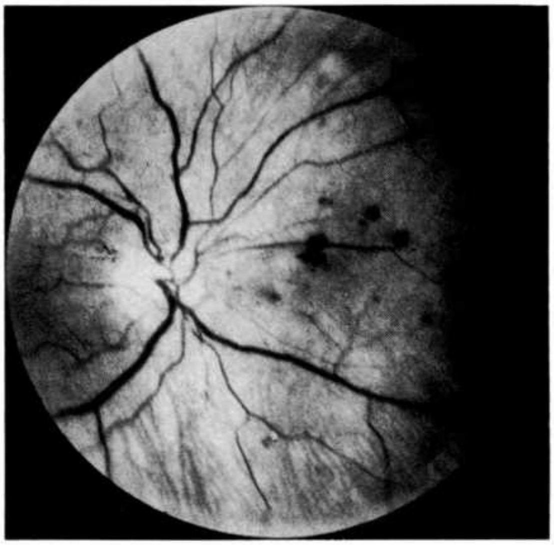

Fig. 3 *Venous stasis retinopathy (case 2) well marked in nasal quadrant.*

rubeosis iridis, and an unreactive dilated pupil. Fundal examination showed venous stasis retinopathy and cotton-wool spots.

Carotid auscultation was hindered by an aortic valve murmur, but intravenous digital subtraction angiography showed arch atheroma with left common carotid artery occlusion.

Eight months after the patient's initial presentation the left VA was PL, with a complicated cataract and rubeotic glaucoma. The IOP was 25 mmHg.

CASE 4

A man aged 66, a hypertensive recovering from a right hemiparesis, was found to be diabetic on

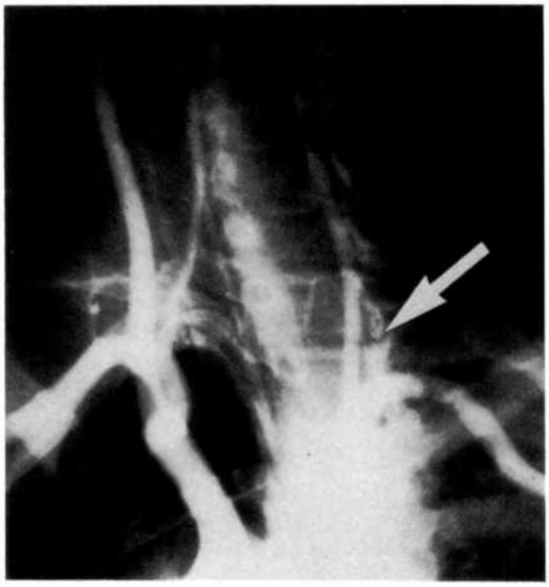

Fig. 2 *Arch aortogram (case 1) showing occluded left common carotid artery (arrow).*

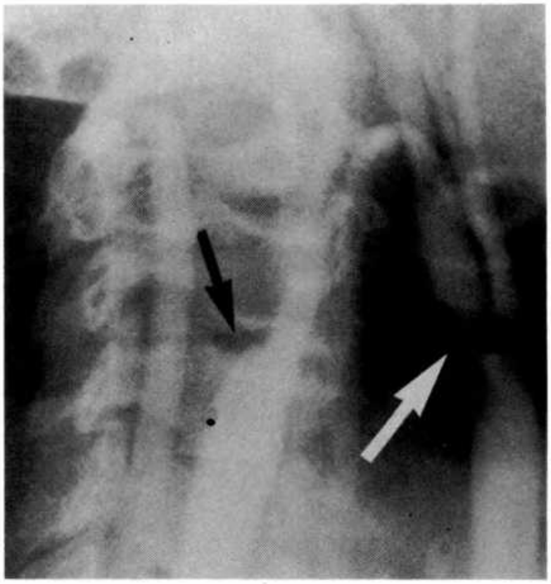

Fig. 4 *Carotid angiography (case 2) shows right internal carotid occlusion (black arrow) with left internal carotid stenosis (white arrow).*

presentation. He complained of left-sided floaters following an episode of amaurosis fugax. His VA was 6/18 right, 6/12 left, with bilateral rubeosis iridis and IOPs of 20 mmHg right, 24 mmHg left. Both fundi showed only mild background diabetic change. In addition there was a left vitreous haemorrhage emanating from the disc.

Two months later he complained of pain over the left eye. His VA was CF, with anterior chamber flare and rubeotic glaucoma, with an IOP of 35 mmHg. A full retinal laser photocoagulation was carried out in this eye. After a further four months the VA on the right had fallen to 6/36, and a right macular branch vein occlusion was noted. The left fundus showed the appearance of an old central retinal artery occlusion associated with a pale disc. Rubeosis iridis was marked bilaterally.

He was experiencing episodes of disorientation. Bilateral carotid bruits were noted, but intravenous digital subtraction angiography was not helpful.

Eighteen months after initial presentation his VA was hand movements right, PL left, with complicated cataracts and rubeotic glaucoma bilaterally (Fig. 5).

CASE 5

A man aged 55, a diabetic with hypertension and angina pectoris, presented with episodes of upper field amaurosis in his amblyopic right eye. His VA was 6/60, with an upper macular branch artery occlusion. Six months later he complained of 'coloured lights' affecting central vision, precipitated by straining. Soon afterwards he returned with a right vitreous haemorrhage and disc new vessels. Episcleral injection, anterior uveitis with posterior synechiae, and early PAS were noted. Despite partial retinal laser photocoagulation, gross proliferative retinopathy with traction detachment ensued (Fig. 6). At around this time he suffered two left-sided hemipareses.

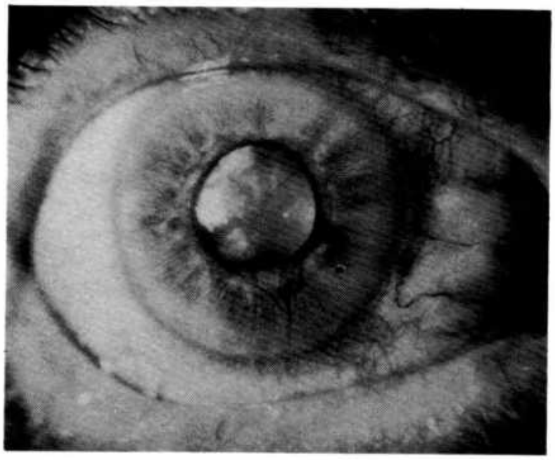

Fig. 5 *End stage of rubeotic glaucoma with secondary cataract (case 4).*

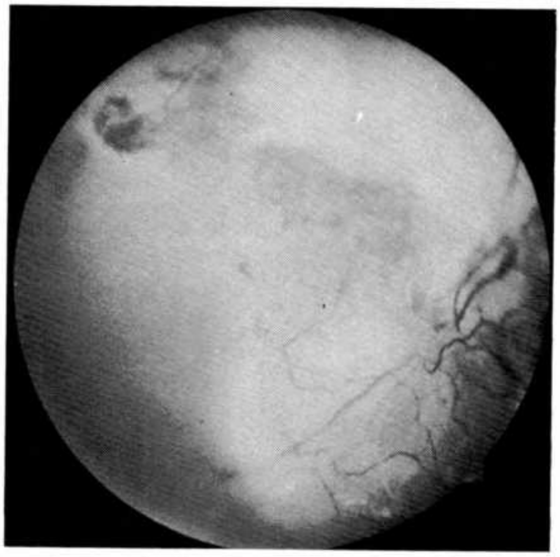

Fig. 6 *Gross proliferative retinopathy (case 5) in diabetic patient whose fellow eye showed minimal change.*

On review two years after his initial presentation he gave a history of persisting positive scotomata in the left eye, particularly on waking. His VA was 6/9, and examination of this previously normal eye showed the appearance of venous stasis retinopathy.

Bilateral carotid bruits were detected. Angiography revealed occlusion of the right internal carotid artery, with tight stenoses of the left internal and external carotid arteries.

CASE 6

A man aged 77, a hypertensive and an ex-smoker, presented with episodes of left upper field amaurosis fugax and blurring of vision. He also complained of seeing bright flashes of light and persisting after-images likened to 'a bright map of Australia'. His VA was 6/5 and no ocular abnormality was found. Fifteen months later he returned with a VA of 6/24 in this eye. Fine rubeosis of the pupil margin, gross disc new vessels (Figs. 7A, B) and peripheral blot haemorrhages on the retina were apparent. A full retinal laser photocoagulation caused only a temporary regression of the disc new vessels. After a further three months he complained of blurred right vision, and this eye also showed venous stasis retinopathy with disc new vessels.

A right carotid bruit was heard. Carotid angiography showed bilateral internal carotid stenoses, more marked on the right, and in addition bilateral

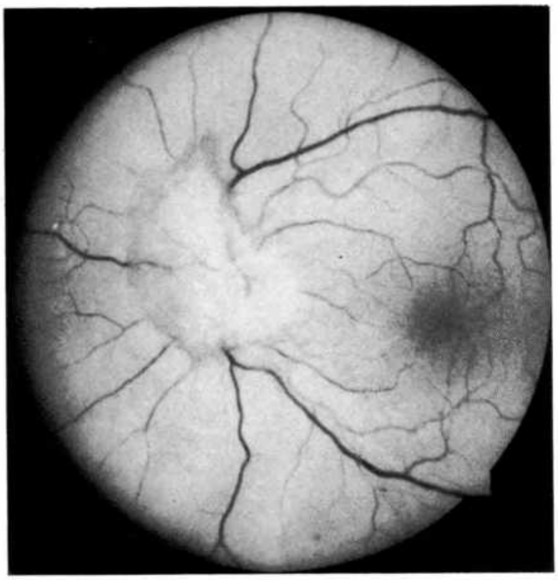

Fig. 7A *Left red free photograph showing gross disc neovascularisation (case 6).*

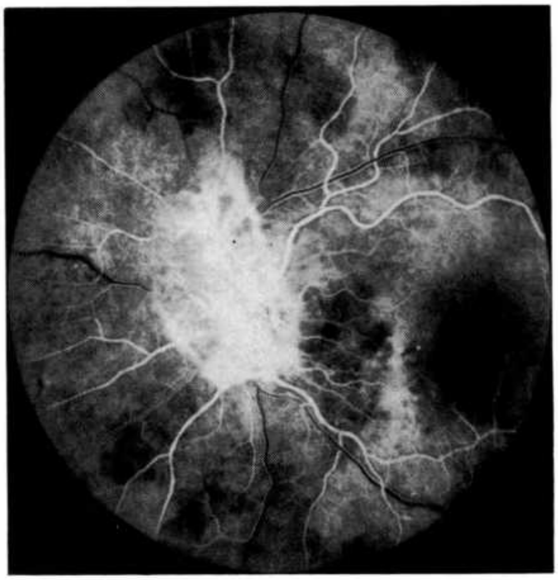

Fig. 7B *Fluorescein angiogram shows leakage of disc new vessels associated with slow irregular choroidal filling.*

external carotid stenoses were present, more marked on the right (Fig. 8).

The case reports are summarised in Table 1.

Discussion

Because the time sequence of events is relatively short prompt investigation of patients presenting with symptoms and signs of chronic ocular ischaemia is desirable, as early intervention may offer hope of therapeutic effect. For this reason a high index of suspicion is necessary.

The visual symptom of note was the description of positive after-images on exposure to bright light, described variously by our patients as 'jagged gold lights', 'coloured lights', and 'a bright map of Australia'. Ross-Russell and Page[2] have previously drawn attention to positive scotomata in patients with carotid artery obstruction. Furlan *et al.*[3] reported five such patients who complained of blurring of vision after exposure to sunlight. Brindley,[4] investigating positive after-images, concluded that after the first few seconds these were due to photochemical effects. Possibly choroidal vascular insufficiency leads to compromise of photoreceptor metabolism.

The signs of chronic anterior segment ischaemia[5] have been well documented in the context of the changes seen after extensive extraocular muscle surgery.[6] Our patients showed episcleral injection, anterior uveitis, and iris atrophy. Iris angiography confirmed ischaemia (case 2). Of six eyes with inflammatory signs four had rubeotic glaucoma, a sign which has not been reported after acute anterior segment ischaemia.[5] Neovascularisation of the iris may follow release of vasoproliferative agents, anteriorly from chronically ischaemic iris and posteriorly from ischaemic retina and choroid.[7] The eyes with rubeosis had relatively low IOPs (25–35 mmHg), which we think are explained by low perfusion pressures[1] causing reduced ciliary body blood flow. Pain in this syndrome[1 8 9] is probably related to ischaemia rather than to increase of IOP.

Venous stasis retinopathy, described by Kearns and Hollenhorst[9] and consisting of venous dilatation, microaneurysms (Fig. 1), and blossom haemorrhages (Fig. 3), is the commonest ocular sign of chronic ischaemia in carotid obstruction, reported in up to 20%[9 10] of cases.

The haemorrhages are larger and darker than those of diabetic retinopathy, are found in the midperiphery, and may be limited to one quadrant. In addition cotton-wool spots may be seen. Disc neovascularisation (Fig. 7) has been described more recently[8] as a response to chronic ischaemia of the retina and choroid (Fig. 7B). Diabetic patients present special diagnostic difficulty, for early stasis retinopathy is difficult to recognise. Important clues are marked asymmetry of retinopathy[8] (Fig. 6) and gross disproportion in the extent of anterior and posterior segment pathology (case 4).

Earlier reports of chronic ocular ischaemia showed most patients to have aortic arch disease, with loss of peripheral pulses[1,11] due to atheroma, Takayashu's pulseless disease,[12,13] or syphilitic aortitis. In our patients the major factor was atheroma affecting the carotid systems. Four of them had central nervous system involvement consistent with carotid artery disease, three of them having had a completed stroke. Amaurosis fugax is the commonest ocular symptom of carotid occlusive disease, and was described by four patients. The manifestations of chronic ocular ischaemia are far less common, and, although they may coexist, patients presenting with amaurosis fugax are not particularly likely to develop chronic ischaemic signs.

Many diagnostic techniques are available for carotid investigation. Ophthalmodynamometry and ocular plethysmography assess carotid artery patency by measurement of the ophthalmic artery pulse pressure. The latter is the more useful test if bilateral lesions are present.[14] The dynamic response to carotid artery compression may be monitored tonographically.[15] Continuous wave Doppler[16] is helpful in establishing whether a significant stenosis is present at the carotid bifurcation, and has the advantage of being non-invasive. Real-time ultrasound[16] can reveal the presence of atheromatous plaques even if they do not have a significant haemodynamic effect. If no carotid artery lesions are present, or if the patients have cardiac arrhythmias, cardiac echography[17] should be carried out to exclude emboli of cardiac origin. Arteriography is the most reliable method of demonstrating carotid artery lesions, but this carries a complication rate of up to 3.7%.[18] Intravenous digital subtraction angiography is safer and has been reported in as many as 96%[18] of selected cases to show a lesion at the carotid bifurcation.

Our findings were similar to those of Brown *et al.*[8] There was either common carotid occlusion on the affected side (Fig. 2) or bilateral internal carotid obstruction (Fig. 4). The patients with bilateral ocular involvement showed a combination of internal and external carotid stenoses (Fig. 8). The pattern of carotid disease seems to be aetiologically important in the development of chronic ocular ischaemia. Huckman and Haas[19] have reported two cases in which there was reversal of flow in the ophthalmic artery, and have suggested there may be a 'steal' syndrome. However, this reversal of flow is a common finding in internal carotid obstruction, and one of our patients (case 6) has orthograde flow in the left and retrograde flow in the right ophthalmic artery, yet shows bilateral ocular ischaemia.

Stenosis of the origin of the internal carotid artery can be relieved by endarterectomy. However, internal carotid occlusion cannot be dealt with in this way, as retrograde thrombosis up to the level of the ophthalmic artery occurs. By taking advantage of the external carotid supply it may instead be by-passed with an anastomosis of the superficial temporal artery to a carotid branch of the middle cerebral artery.[20]

Table 1 *Summary of the case reports*

Case no	General health Age	CNS involvement	Angiography results	Eye	Amaurosis	Ischaemic visual symptoms	Episcleral injection and/or anterior chamber activity	Rubeotic glaucoma Low IOP	Ischaemic pain	Venous stasis	Disc new vessels
1	Hypertension, angina, smoker, 39 yr	Transient ischaemic attacks, R side	L CC occluded	LE	+	+	+	–	+	+	+
2	Smoker, 55 yr	Light-headed, unwell	R IC occluded L IC stenosed	RE	–	–	+	+	+	+	+
3	Hypertension, smoker, 67 yr	R CVA	L CC occluded	LE	–	+	+	+	+	+	–
4	Hypertension, diabetes, 66 yr	R CVA, episodes of confusion	•	LE	+	–	+	+	+	–	+
				RE	+	–	+	+	–	–	–
5	Hypertension, angina, diabetes, 55 yr	L CVA × 2	R IC occluded L IC + EC stenosed	RE	+	+	+	–	+	–	+
				LE	–	+	–	–	–	+	–
6*	Hypertension, ex-smoker, 77 yr	Nil	Bilateral IC + EC stenosed	LE	+	+	–	–	–	+	+
				RE	–	+	–	–	–	+	+

*This patient's left eye showed fine rubeosis of the pupil margin CNS=central nervous system CVA=cerebrovascular accident CC=common carotid artery. IC=internal carotid artery EC=external carotid artery

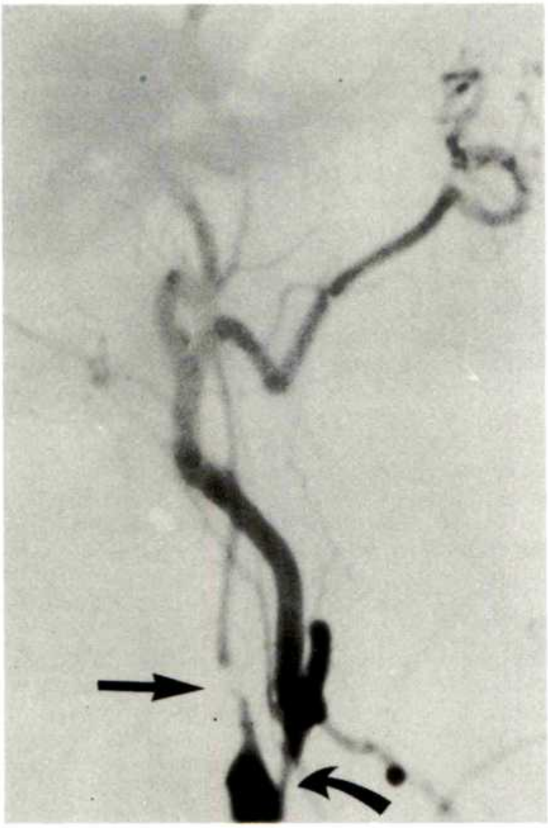

Fig. 8 *Subtraction angiogram (case 6) showing right internal (straight arrow) and external carotid stenoses (curved arrow).*

This may not be feasible if the external carotid artery itself is also severely affected. Several case reports of successful by-pass surgery for the relief of ocular ischaemia have been published.[10,21-23]

Laser retinal photocoagulation was ineffective in the treatment of disc neovascularisation in our patients. The possibility exists that in established rubeosis, given that ischaemia can be relieved surgically, trabeculectomy may control ocular hypertension, as can occur in the management of diabetic neovascular glaucoma.[24] By the end stage of this syndrome with rubeotic glaucoma, secondary cataract (Fig. 5) and probably occult central retinal artery occlusion,[8] nothing can be done except for the relief of ischaemic pain,[10] Recorded attempts at lens extraction[1,2] show this to be unsuccessful.

The syndrome of ocular inflammation secondary to chronic ischaemia is uncommon, and neither ophthalmologists nor other specialists dealing with patients with carotid artery disease have much experience of the condition. Its diagnosis is made more difficult because it causes a plethora of signs and has to be differentiated from other causes of decreased visual acuity, ocular pain, teichopsia, anterior uveitis, rubeotic glaucoma, retinal venous dilatation with haemorrhages, and disc new vessel formation. Early recognition of the syndrome of chronic ocular ischaemia is important because there is now hope of useful improvement by reconstructive vascular surgery in the initial stages, while treatment later on fails to halt progression of the disease.

We extend our thanks to Lynn Griffin for her secretarial assistance, to the Department of Retinal Photography at Manchester Royal Eye Hospital, and to the Department of Medical Illustration at Manchester Royal Infirmary.

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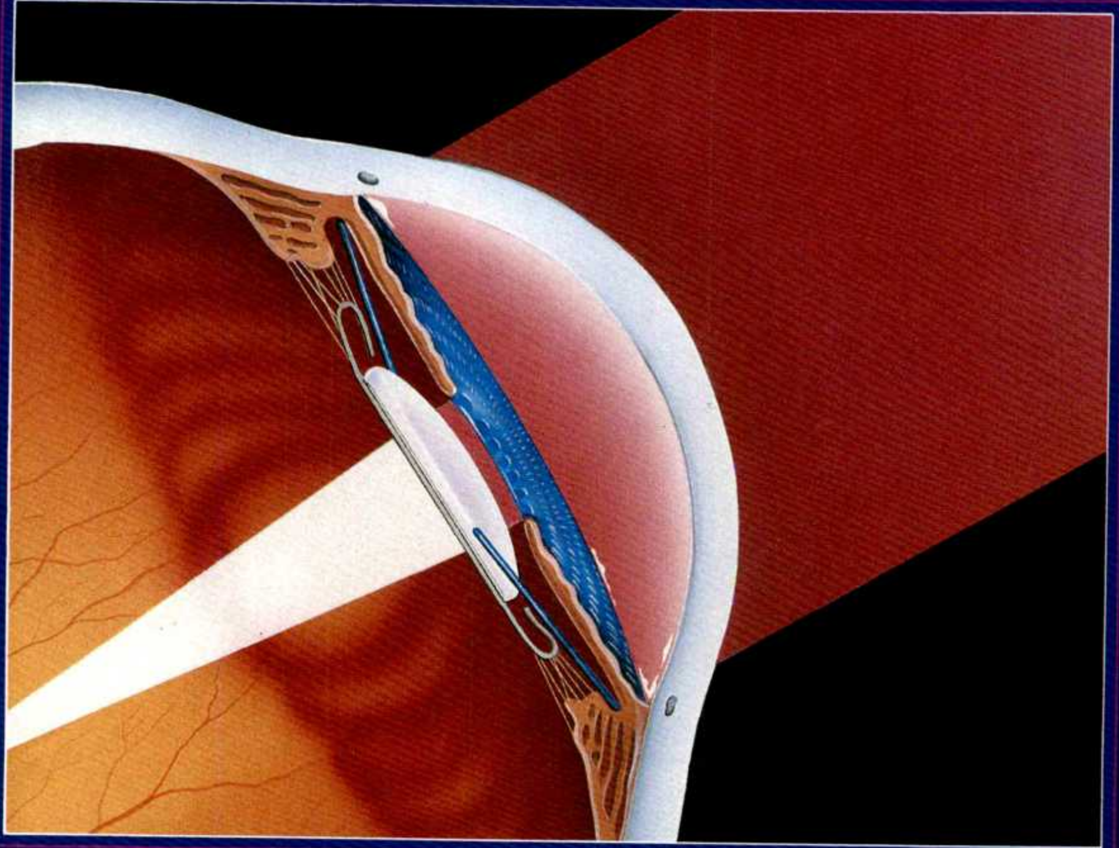

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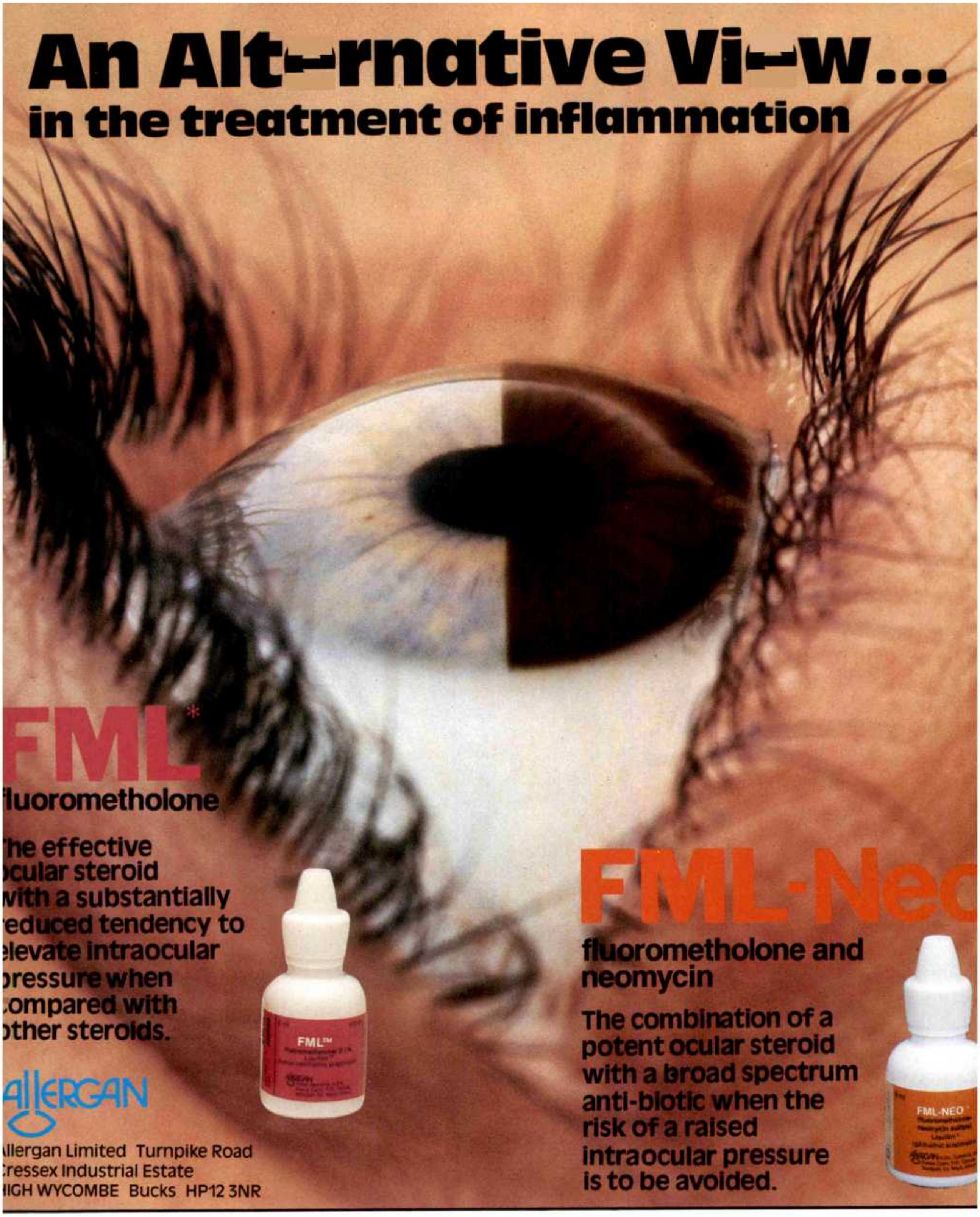

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risk of a raised
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is to be avoided.

PRESCRIBING INFORMATION
entation White, microfine, sterile ophthalmic suspension containing fluorometholone (0.1%). **Uses** Topical ophthalmic
ension for steroid responsive inflammation of the palpebral and bulbar conjunctiva, cornea and anterior segment of the
e. **Dosage and Administration** 1 to 2 drops instilled into the conjunctival sac two to four times daily. During the initial 24 to
ours the dosage may be safely increased to 2 drops every hour. Care should be taken not to discontinue therapy prematurely.
tra-indications, Warnings, etc. CONTRA-INDICATIONS. Acute superficial herpes simplex keratitis. Fungal diseases of ocular
ctures. Vaccinia, varicella and most other viral diseases of the cornea and conjunctiva. Tuberculosis of the eye. Hypersensitivity
e constituents of this medication. **Warnings** Steroid medication in the treatment of herpes simplex keratitis (involving the
mal requires great caution; frequent slit-lamp microscopy is mandatory. Prolonged use may result in glaucoma, damage to the
c nerve, defects in visual acuity and fields of vision, posterior subcapsular cataract formation, or may aid in the establishment of
ndary ocular infections from fungi or viruses liberated from ocular tissue. In those diseases causing thinning of the cornea or
a, perforation has been known to occur with use of topical steroids. Safety and effectiveness have not been demonstrated in
ren of the age group two years or below. This preparation contains benzalkonium chloride and should be used with caution in
ciation with hydrophilic contact lenses. **Use in Pregnancy** Safety of the use of topical steroids during pregnancy has not been
blished. **Precautions** As fungal infections of the cornea are particularly prone to develop coincidentally with long-term steroid
ications, fungus invasion must be suspected in any persistent corneal ulceration where a steroid has been used or is in use. Intra
ar pressure should be checked frequently. **Adverse Reactions** Glaucoma with optic nerve damage, visual acuity or field defects,
erior subcapsular cataract formation, secondary ocular infection from pathogens liberated from ocular tissues, perforation of
globe. Local side effects of steroid therapy, ie skin atrophy, striae and telangiectasia, are especially likely to affect facial skin.
maceutical Precautions Protect from freezing. **Legal Category** POM. **Package Quantities** Supplied in plastic dropper

FML-NEO* PRESCRIBING INFORMATION
Presentation Sterile, white, microfine ophthalmic suspension containing fluorometholone, NF0.1% and neomycin sulphate
BP0.5% (equivalent to 0.35% neomycin base). **Uses** FML-NEO* is indicated for the management of steroid responsive inflamm
the palpebral or bulbar conjunctiva, cornea and anterior segment of the globe, when threatened or complicated by infectio
neomycin-sensitive organisms. **Dosage and Administration** One or two drops in the conjunctival sac two to four times dai
During the initial 24 to 48 hours, the dosage may be safely increased to one drop every hour. Care should be taken not to disc
treatment prematurely. Shake well before using. **Contra-indications, Warnings etc.** Acute untreated purulent ocular infect
Acute superficial herpes simplex (dendritic keratitis), vaccinia, varicella and most other viral diseases of the conjunctiva and
Ocular tuberculosis, fungal diseases of the eye and hypersensitivity to any of the components of the drug. **Warnings** As for F
above and, in addition in diseases due to micro-organisms resistant to neomycin, infection may be masked enhanced or acti
the steroid. Prolonged use may result in overgrowth of nonsusceptible organisms. Articles in current medical literature indi
increase in the prevalence of persons sensitive to neomycin. The possibility of such a reaction should be borne in mind. If se
or other untoward reactions occur discontinue the medication. **Precautions** Patients with histories of herpes simplex kera
should be treated with caution. Use of topical steroids may increase intraocular pressure. Safety of intensive or protracted u
topical steroids during pregnancy has not been substantiated. Local side effects of steroid therapy, ie skin atrophy, striae an
telangiectasia, are especially likely to affect facial skin. **Pharmaceutical Precautions** Shake well before using. Do not freez
Category POM. **Package Quantities** Available in 5ml plastic dropper bottles. Basic NHS cost (as at July 1984) £1.90. PL 0426/0
Prescribing information is available on request.

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Transient monocular obscuration—? amaurosis fugax: a case report

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SUMMARY A 73-year-old white man with pseudophakia experienced repeated bouts of transient visual loss associated with erythropsia and colour desaturation. A diagnosis of atheromatous carotid vascular disease was considered, prompting carotid angiography, during which time the patient experienced transient aphasia. Subsequent examination during an episode of visual loss showed that a spontaneous anterior chamber haemorrhage was the cause of the visual complaints.

The complaint of transient bouts of monocular visual loss in an older person suggests the presence of atheromatous disease of the carotid arteries and the necessity for neuroradiological examination. The symptoms during an attack of transient monocular visual loss may suggest various diagnoses and obviate the need for such studies, with their inherent risk. A patient with complaints of recurrent bouts of transient monocular visual loss and suffering from temporary speech arrest followed by mild aphasia subsequent to carotid angiography is the subject of this report.

Case report

A 73-year-old white man began experiencing bouts of transient visual blurring affecting the right eye eight months before his initial examination. During these eight months repeated examinations by his ophthalmologist while the patient was asymptomatic failed to reveal any ocular pathology. He was referred to an internist and then to a neurologist for evaluation of 'amaurosis fugax.' Venous subtraction angiography revealed irregularities in the area of the left carotid bifurcation. Subsequent carotid angiography showed ulceration and mild stenosis of the left internal carotid artery at the bifurcation and a 50% stenosis of the carotid siphon on the left side. The right carotid bifurcation was normal, there was only moderate narrowing of the siphon, and no ulceration was seen. During the carotid angiography, after repositioning the catheter in the aortic arch, the patient noted he was unable to talk for a short time, and several minutes of aphasia followed. After this episode a computerised axial tomogram was normal. The patient was treated with dipyridamole (Persantine) and aspirin without any alteration in his symptoms.

Elucidation of the patient's history revealed that the episode of so-called monocular visual loss consisted of a sensation of 'foggy vision' associated with erythropsia (seeing red) and colour desaturation, especially for the colour red. He specifically denied total blackouts or a curtain. These episodes initially lasted 15–20 minutes and occurred once a month, but by the time of his referral his longest episode had lasted seven hours and the frequency had increased to three to four bouts per week. The episodes were sudden in onset and unassociated with any neurological symptoms such as weakness, numbness, dysarthria, diplopia, headache, or orbital pain. No precipitating events could be identified. According to his medical history he had had an intracapsular cataract extraction with iris fixation lens implant in the left eye in 1973, and a similar procedure had been performed in the right eye in 1980, both without complications. Topical 2% pilocarpine had been used intermittently to stabilise the lens in his right eye. He also had a history of hypertension for 10 years, treated with chlorothiazide (Diuril), and arthritis occasionally treated with aspirin.

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Examination at the time of referral showed a visual acuity of 20/20 in the right eye and 20/15 in the left eye at distance. His right pupil was 3 mm, square (from an iris fixation implant), and non-reactive. The left pupil was 4 mm and minimally reactive. The results of tests of optic nerve function, brightness and colour comparison, and American Optical colour plates were equal and normal bilaterally. Amsler grid testing revealed no defects. Slit lamp examination showed well healed anterior segments on both sides. The intraocular lens implants did not come close to any angle structures, and the foot processes were not associated with any iris or pupillary lesions. Applanation pressures were 18 mmHg in the right eye and 21 mmHg in the left. Visual field testing by kinetic perimetry was normal. Gonioscopy performed at this time revealed an abnormal sheath of vessels near the iridectomy in the superior angle of the right eye. Ophthalmodynamometry was 60 mmHg in both eyes.

The patient was subsequently seen again during an attack of blurred vision. Examination then revealed diffuse anterior chamber haze secondary to a considerable number of erythrocytes in the aqueous, which were also found to be layered on the corneal endothelium. In addition gonioscopy performed then showed blood streaming from the previously noted vessels in the superior chamber angle and a microscopic hyphaema in the inferior angle. The patient refused fluorescein angiography because of a possible allergy to contrast material.

Discussion

The classic features of amaurosis fugax include sudden painless visual loss in one eye which lasts from 30 seconds to 15 minutes (usually 2 to 3 minutes) and then vision returns.[1] The visual loss may be total or partial, often being described as a 'shade effect' marked by a sharp horizontal border involving the upper or lower hemifield. The implication of this type of monocular visual disturbance is that of ipsilateral carotid atherosclerotic disease with or without ulceration, producing either a cholesterol plaque or a platelet fibrin embolus which lodges in the central retinal artery or one of its main branches. Thus, when the clinician hears that a patient has had bouts of transient monocular visual loss, he often immediately begins an investigation of the carotid system, including angiography with all of its attendant risks.

Our patient described the sudden onset of painless, recurrent monocular visual disturbance which consisted of erythropsia, colour desaturation, and a fogginess of his vision. The duration of symptoms ranged from 15 minutes to seven hours. These symptoms are in sharp contrast to those of classic amaurosis fugax. To our knowledge, the complaint of erythropsia has not been reported with amaurosis fugax, and it should suggest either intraocular haemorrhage or bleaching of the aphakic or pseudophakic retina after exposure to bright sunlight. In addition, most patients with occlusive carotid disease and amaurosis fugax experience other concomitant transient neurological symptoms, though a small percentage will have only visual complaints. Thus, the lack of associated neurological symptoms in our patient suggests, but is not diagnostic of, a normal carotid circulation. The history is thus the key to suspecting the diagnosis of an anterior chamber haemorrhage. Most often when the patient is asymptomatic the ophthalmological examination will be entirely normal. In fact the anterior chamber may clear within hours of a symptomatic haemorrhage.[2] Therefore the clinician needs a high index of suspicion of the possibility of a transient anterior chamber haemorrhage.

The causes of spontaneous anterior chamber haemorrhages are numerous (Table 1). Such haemorrhages may be seen as a late complication of cataract surgery due to ruptured incisional vessels,[3,4] iris or angle neovascularisation, peripupillary microangiomas, coagulation disorders, or anticoagulation medication.[5] In addition the implantation of an intraocular lens compounds the problem depending on the type of lens used. For example, the uveitis-glaucoma-hyphaema (UGH) syndrome[6,7] may be produced by rigid anterior chamber lenses. Peri-

Table 1 *Causes of spontaneous anterior chamber haemorrhages*

Vascular anomalies of the iris
  Myotonic dystrophy[11,12]
  Sturge-Weber syndrome[13]
  Microhaemangiomas
  Diffuse haemangiomatosis of childhood[14]
Neoplasms
  Melanoma
  Retinoblastoma[13]
Diseases of the blood or vessels
  Leukaemia[13]
  Haemophilia[13]
  Scurvy[13]
  Lymphoma[15]
Rubeosis iridis[16]
Severe iritis[13,16]
Fibrovascular membranes
Juvenile xanthogranuloma[16]
Occult trauma or delayed bleeding after trauma[16]
Hydro-ophthalmos[17]
Malignant exophthalmos[13]
Histiocytosis X[18]
Postsclerotomy with cautery[19]
Postcataract surgery bridging wound vessels[3]; irritative phenomenon with neovascular tufts associated with intraocular lenses[9,20]

pupillary iris erosion associated with either pupillary plane or posterior chamber lenses may produce similar clinical findings.[8-10]

In our case an abnormal tuft of vessels was noted near the iridectomy at the time of initial examination, and this proved to be the site of haemorrhage when the patient was examined during a bout of visual blurring. The cause of the neovascular tuft of vessels in this location is not clear. If the diagnosis of spontaneous intraocular haemorrhage had been made earlier, angiography with its associated risks might have been obviated. The clinician should be aware of the possibility of spontaneous anterior chamber haemorrhage as a cause of transient monocular visual disturbance. Erythropsia should arouse the suspicion of intraocular haemorrhage. Ophthalmological examination, preferably while the patient has symptoms, may be diagnostic and obviate the need for invasive and potentially dangerous studies.

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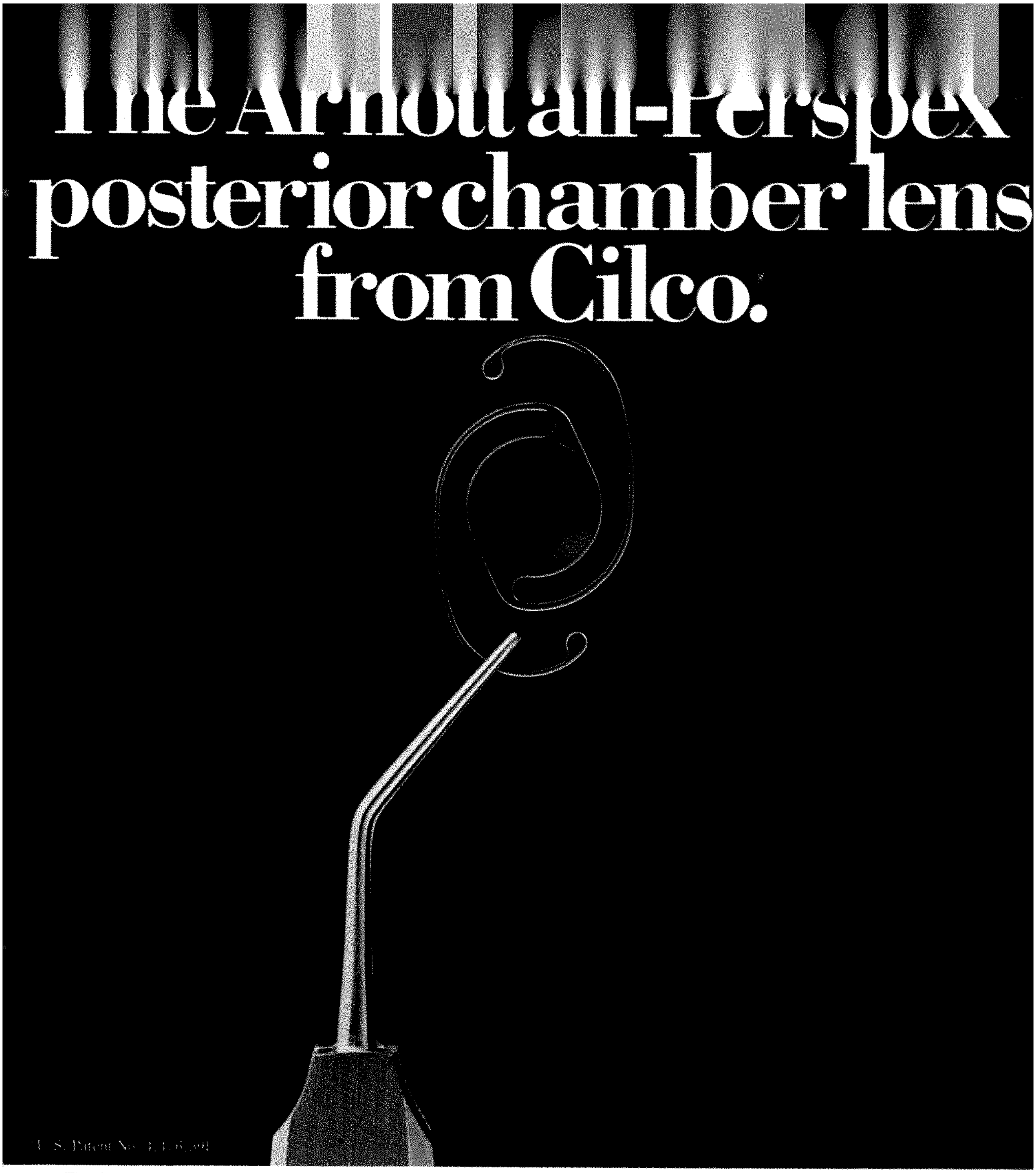

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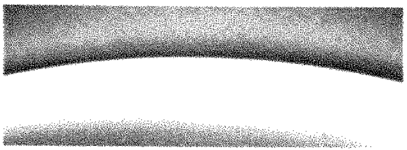

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Bilateral macular dysplasia ('colobomata') and congenital retinal dystrophy

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SUMMARY Three unrelated patients with bilateral macular dysplasia ('colobomata') with no relevant family history were found to have absent or substantially abnormal electroretinograms, implying that there was an associated retinal dystrophy. This may suggest that the macular lesions are associated with a global failure of retinal development, with a regional preponderance rather than a purely localised cause such as an intrauterine infection. It is important to distinguish between congenital infections such as toxoplasmosis and developmental macular colobomata, which have a somewhat similar ophthalmoscopic appearance as a cause of bilateral macular abnormalities seen in young children, since they have different implications for genetic advice and future ophthalmic care.

Until intrauterine infection with *Toxoplasma gondii* was recognised as a cause of certain congenital macular abnormalities and serological tests for toxoplasmosis became available, many macular lesions which are now more readily diagnosed as those of congenital toxoplasmosis were classified as congenital macular 'colobomata.' Ida Mann pointed out that not only were most of these cases due to intrauterine infection, but the term macular 'coloboma' is itself a misnomer, as it does not result from a defect in closure of the fetal fissure.[1] The term macular dysplasia may be preferable. There is, however, a group of patients with bilateral macular 'colobomata' or dysplasia, in whom the defect is thought to result from an abnormality of development of the macula unrelated to fetal fissure closure defects. A developmental mechanism is likely in those cases with a family history, or when there are other systemic abnormalities which form part of a recognisable syndrome. It may not be possible to distinguish between inflammatory and developmental aetiology on clinical appearance alone.[2]

Bilateral macular 'colobomata' have been described in sibs[3-6] and in two or more successive generations,[2 7-10] and have been reported in association with two different systemic abnormalities. Such an association has been proposed as evidence of primary developmental aetiology for the macular lesions. Sorsby[2] described a family group consisting of a mother and five children all of whom had bilateral pigmented 'colobomata' in association with a rare skeletal abnormality—apical dystrophy of the hands and feet. Bilateral macular 'colobomata' have also been described in idiopathic infantile hypercalcuria.[11 12] This condition may be inherited in an autosomal recessive manner, as it has been reported in two sibs from a consanguineous marriage.[11]

A third group of patients with macular 'colobomata' have electrophysiological evidence of a more widespread retinal dystrophy. An absent or abnormal electroretinogram has been reported in association with familial macular 'colobomata'[3 9] and in 'colobomata' associated with idiopathic infantile hypercalcuria.[11] Macular 'colobomata' and an absent electroretinogram have also been reported in Leber's amaurosis[13 14] and retinitis pigmentosa.[15 16] Not all familial cases have abnormal electrodiagnostic tests, however. Tamaki *et al.*[10] found a normal electroretinogram, electroculogram, and dark adaptometry in all affected family members in their pedigree of autosomal dominantly inherited macular 'colobomata.'

We present here three cases of bilateral macular dysplasia with abnormal electrodiagnostic findings, in whom the macular lesions are likely to be developmental in origin rather than secondary to intrauterine infection.

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Case reports

CASE 1

This female infant was first seen at the Hospital for Sick Children at 13 months of age. She was the second child born to unrelated parents, and there was no relevant family history. The mother had two upper respiratory tract infections during pregnancy at three and eight months, but the pregnancy was otherwise uneventful. There was a normal delivery at term. At birth the infant was noted to have an extra thumb on the right hand (Fig. 1), but initial examination was otherwise normal. The extra digit was excised at 11 months. At 4 weeks the parents had noticed that the child had 'wobbly eyes' and that her vision appeared very poor. She was seen by a local ophthalmologist, who found poor visual attention, nystagmus, and bilateral macular abnormalities.

When the child was first examined at the Hospital for Sick Children she showed no response to light; there were 'roving eye movements' and absent pupillary responses to light. The anterior segments were normal, but both fundi showed similar abnormal appearances (Fig. 2). Both discs were pale, and the retinal blood vessels were attenuated. There were scattered peripheral retinal pigmentation and bilateral non-pigmented macular 'colobomata.' In the right eye there was an excavated, non-pigmented 'coloboma' with ectatic sclera at the base. A few large choroidal blood vessels were visible at the base, but no retinal vessels crossed the defect. In the left eye there was a non-ectatic macular 'coloboma' with small and medium sized choroidal vessels visible in the base. Again no retinal vessels crossed the defect. General examination was normal apart from a scar at the right thumb. Developmental assessment revealed that she was developing normally for a blind child of her age. There was no recordable electroretinogram or flash visually evoked potential on two occasions (Fig. 3). *X*-ray of the hands and feet showed a short right first metacarpal with an abnormal epiphysis of the terminal phalynx, but was otherwise normal. A CT scan showed high density areas in the retina of both globes, which may represent calcification in the

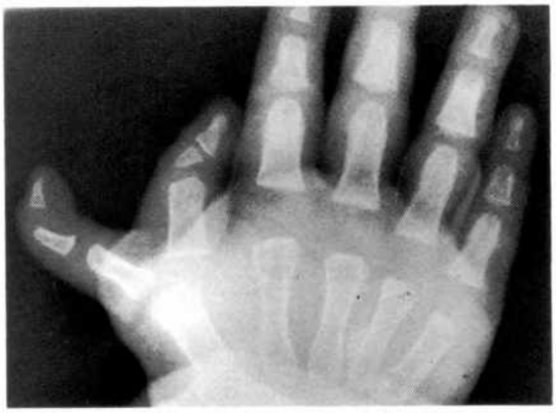


Fig. 1 *Case 1. Plain x-ray of right hand showing polydactylism.*

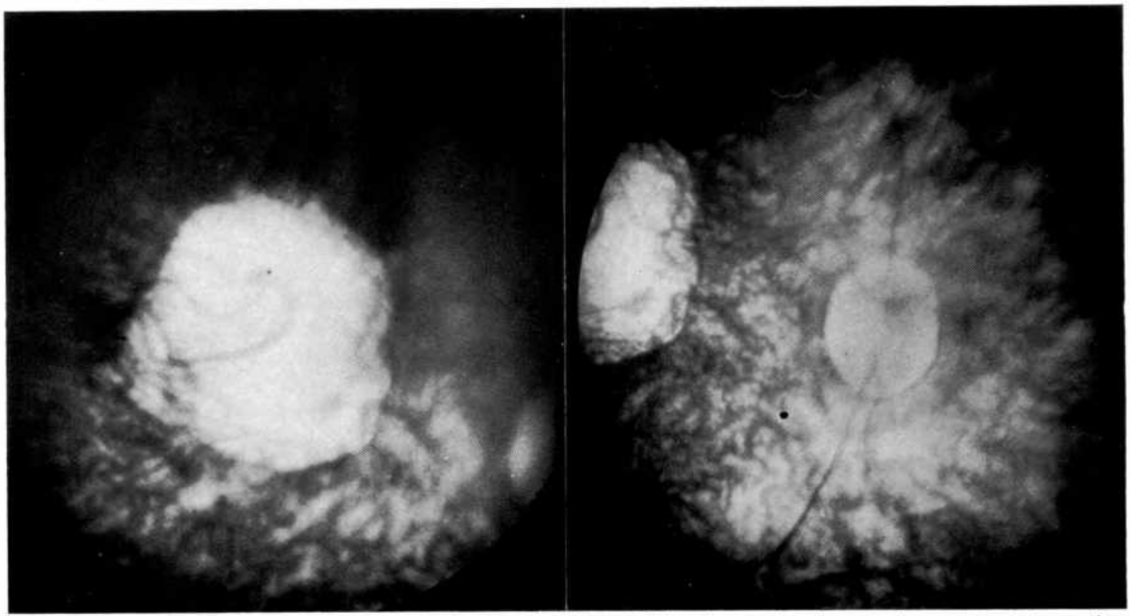


Fig. 2a *Case 1. Fundus photograph of right eye showing pole disc with thready vessels and a non-pigmented ectatic macular coloboma, with a few choroidal vessels in the base.*

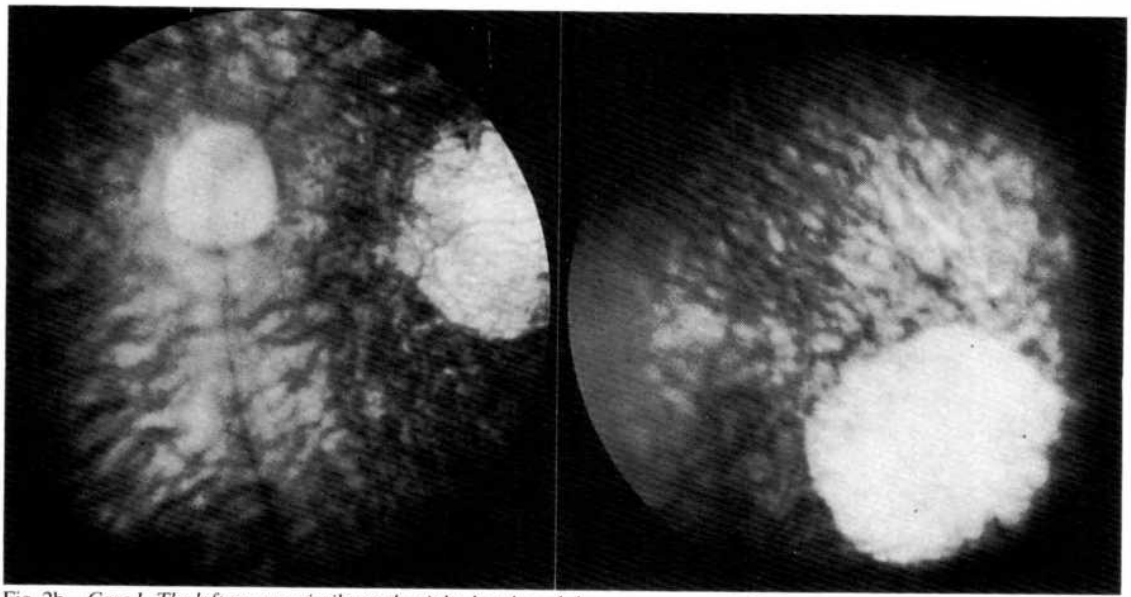


Fig. 2b *Case 1. The left eye was similar to the right, but the coloboma was non-ectatic.*

base of the macular 'coloboma' (Fig. 4), but was otherwise normal. Other investigations including serum and urinary amino acids, urinary reducing substances, urinary calcium excretion, synthetic vasopressin urinary concentration tests, and skull x-ray were normal. Toxoplasma dye test was negative at 1 in 16 dilution in the mother and baby on two occasions. Serological tests for cytomegalovirus, rubella, and herpes simplex were negative in mother and child. The fundi of both parents and her older sibling were examined and found to be normal.

CASE 2

This young girl was first seen at the Hospital for Sick Children at 3 years of age. She is the only child born to unrelated parents and there is no relevant family history. The mother had severe essential hypertension and depression, and was taking methyldopa, propranolol, and amitriptyline during the pregnancy. She required several admissions during the pregnancy, because of the raised blood pressure, and the delivery was at 38 weeks by caesarian section. Birth weight was 2040 g. The placenta was small and there was slight meconium staining at delivery. At 6 weeks her mother had noticed 'wobbly' eyes and thought that her vision was poor. However, over the following months her vision appeared to improve. When the girl was first seen at the age of 3 years there was horizontal nystagmus, with an abnormal head posture and a face turn to the left. There was a right divergent squint, but ocular movements were full. Both fundi were abnormal (Fig. 5). The discs were normal, but the vessels, which were of normal calibre, were dragged temporally to large, deep, non-pigmented macular defects. There was marked bilateral scleral ectasia with a line of pigment and blood vessels stretched across the defect, giving it a bilobed appearance. Large choroidal vessels crossed the base of the 'coloboma' in each eye. General examination had revealed no other systemic abnormalities. She has shown normal intellectual development; though she has been investigated on several occasions for poor weight gain and short stature, no organic cause has been found. A toxoplasma dye test carried out at the age of 6 months was negative at 1 in 16 dilution.

She was last reviewed in May 1983 at the age of 6, when she was managing well at a normal school. Distance visual acuity was 6/36 in each eye and binocular near vision 6/9 on a reduced Snellen chart at 10 cm. There was horizontal nystagmus, an abnormal head posture, with either left or right face turn, and an alternating divergent squint. Colour vision was normal on testing with Ishihara plates in each eye. Visual field examination showed bilateral relative central scotoma with normal peripheral fields. The fundus appearances were unchanged. The electroretinogram was of markedly reduced amplitude (Fig. 3). The flash visually evoked potential was of normal latency and wave form, but the major early component was of reduced amplitude.

CASE 3

This Greek boy was first seen at the Hospital for Sick

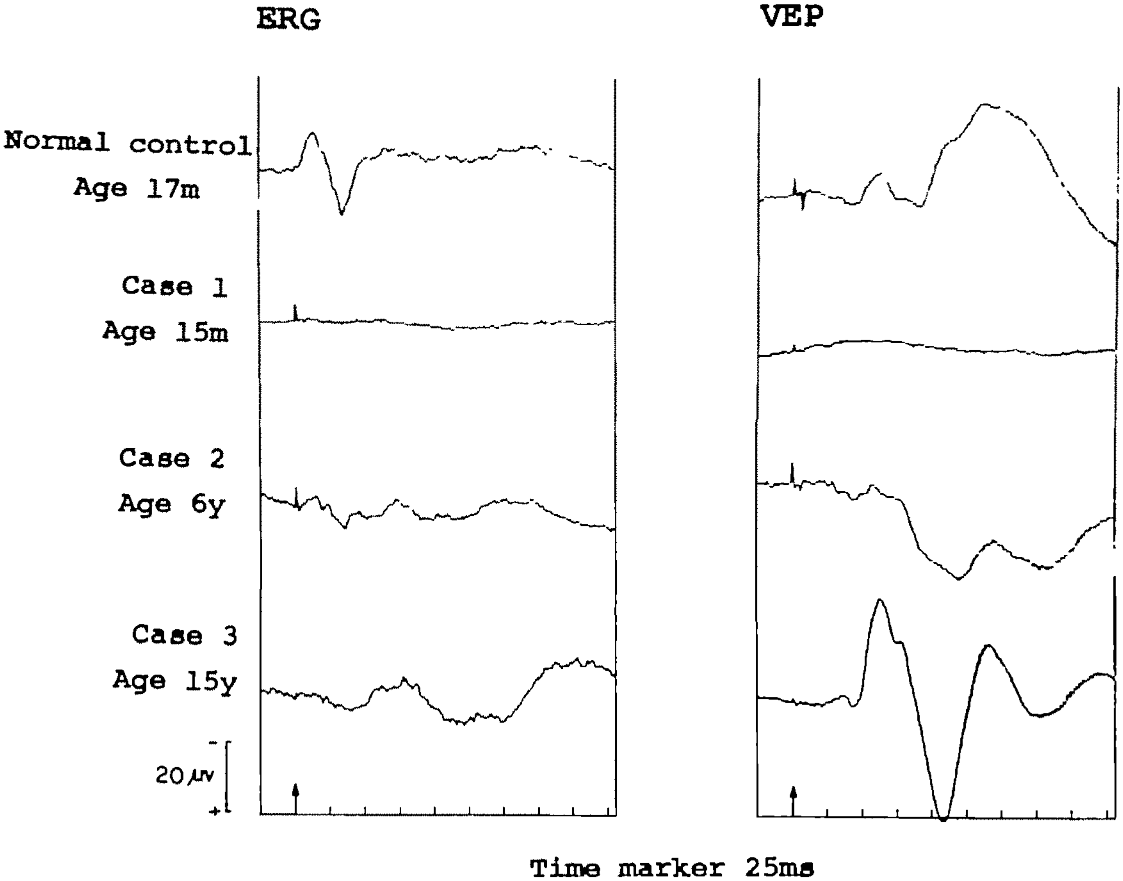


Fig. 3 *ERG (recorded from bridge of nose) and VEP (midoccipital) in response to flash stimulus. Eyes open, both eyes stimulated simultaneously at arrow. Note absent or very poor ERG in cases 1, 2, and 3 compared with normal control. In case 1 no VER is recordable; in case 2 the VEP earlier components in the first 75 ms are small and poorly defined compared with normal. In case 3, however, a well defined VEP is seen which is somewhat unusually large, but within normal limits. These findings contrast with cases of toxoplasmosis retinitis which have not shown gross ERG abnormalities.*

Children at the age of 15 years. He had been referred to Professor Otto Wolff for investigation of renal, metabolic, and respiratory problems. He was born to unrelated parents at 28 weeks gestation. The pregnancy had been normal until that point. Birth weight was 1500 g, and he required oxygen, without mechanical ventilation, for about 30 days. He had poor vision and nystagmus from infancy but was able to attend a normal school, where he was said to be 'slow.' He also had hearing problems and had worn a hearing aid from the age of 6. At 10 years he had been noted to get short of breath very easily, and his respiratory difficulties gradually increased, which led to investigation in Greece. This had revealed polycythaemia, interstitial lung disease, and radiological and biochemical evidence of rickets.

When he was examined in London his visual acuity was 3/60 right and 6/60 left, with +5·00 spherical dioptre correction in each eye. Binocular visual acuity was 6/60 for distance and 6/18 Snellen for near. With a low-vision aid he was able to read a 6/6 reduced Snellen chart at 10 cm. There was manifest horizontal nystagmus and an alternating divergent squint. Ocular movements were full and pupil reactions were normal. Both fundi were abnormal (Fig. 6).

In the right eye there was a deeply excavated macular defect with two large choroidal vessels, one of which appeared to penetrate the sclera in the manner similar to a vortex vein, crossing the base. A thin membrane containing pigment was suspended across the defect at the level of the normal retina. The optic disc was vertically oval and was segmentally hypoplastic, being deficient in the area of the papillo-

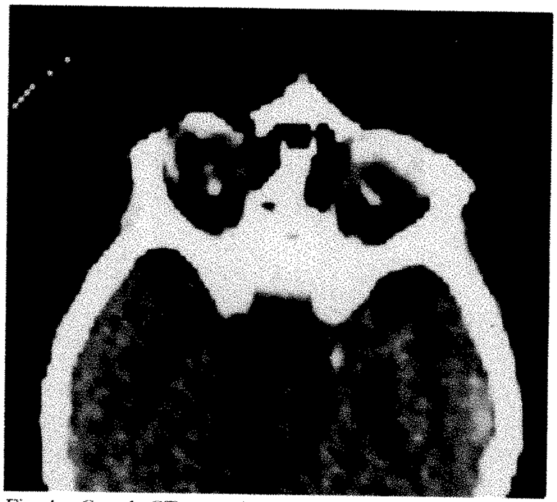


Fig. 4 *Case 1. CT scan (EMI 1010) showing high density areas at both posterior poles.*

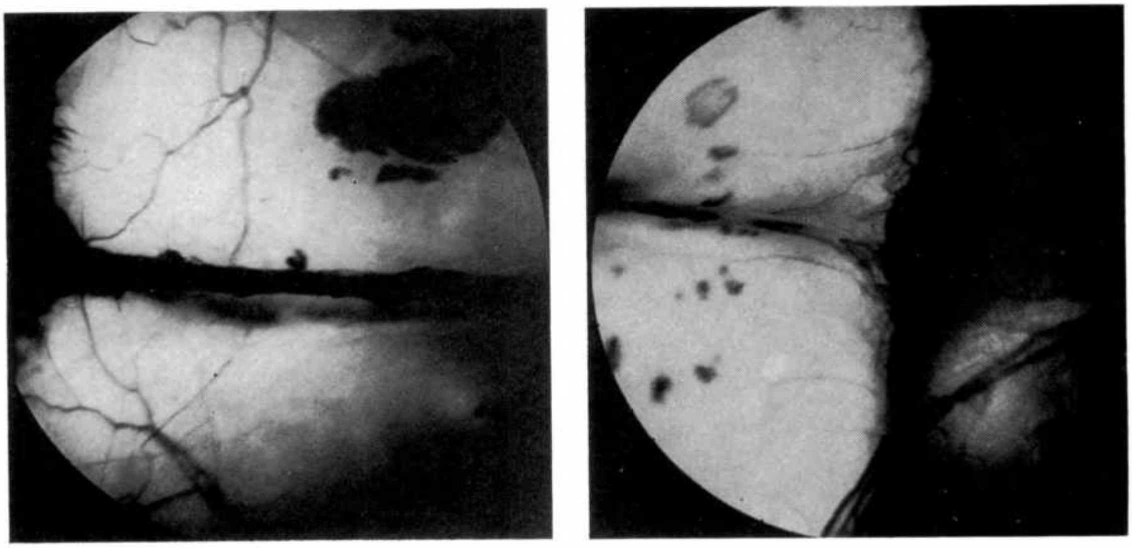
macular bundle—resulting in a kidney-shaped disc. In the left eye the optic disc was similar in shape and there was a large macular defect, but no underlying scleral ectasia. The retinal pigment epithelium and small choroidal vessels were absent in the area of the defect, but medium and large sized choroidal vessels traversed the base. A few retinal vessels crossed the periphery of the lesion. The peripheral retina was normal in each eye. The electroretinogram was reduced in amplitude (Fig. 3). The flash visually evoked potential was well formed and of the usual latency and waveform.

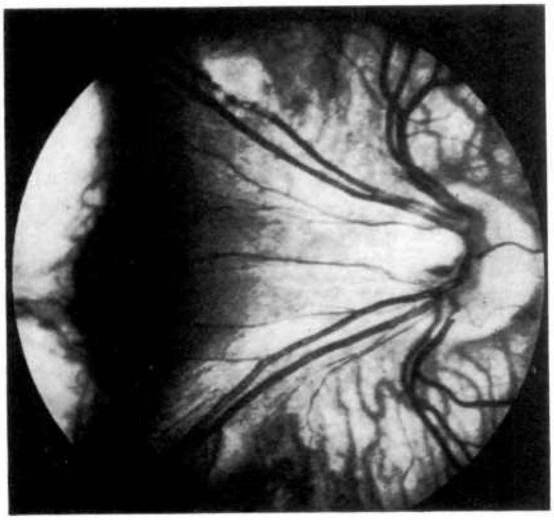
General examination showed that he was below the tenth percentile for both height and weight, and the head circumference was on the third percentile. He was slightly cyanosed, with finger clubbing, but chest examination was normal. He was of subnormal intelligence, had marked genu valgum, but systemic examination was otherwise normal. Extensive investigations were carried out to elucidate the cause of his systemic and ocular problems and to try to provide a single unifying diagnosis. This was not possible. A chest *x*-ray showed the appearance of interstitial lung disease, and lung function tests confirmed that there was a diffusion defect. A lung biopsy, however, was not diagnostic; the histological appearances were consistent either with a viral pneumonia or a disease characterised by circulating immune complexes. Renal investigation revealed renal tubular abnormalities with renal tubular proteinuria, aminoaciduria, glycosuria, and an inability to acidify or concentrate the urine normally. Renal ultrasound and intravenous pyelogram were normal. A renal biopsy showed mild mesangial proliferation and tubular atrophy. There was no interstitial nephritis, and immunofluorescence tests were negative for IgG, IgA, and IgM. A skeletal survey showed radiological evidence of healing rickets. A CT scan showed colpocephaly (Fig. 7). An audiogram revealed bilateral sensorineural hearing loss. A toxoplasma dye test was negative at 1 in 16 dilution, and venereal disease reference laboratory (VDRL) and *Treponema pallidum* haemagglutination (TPHA) tests were negative. Many other investigations including immunological studies and viral serology were negative. No unifying diagnosis was made. He was treated empirically with oral steroids with some improvement in his respiratory function.

Discussion

Ida Mann[1 17] classified macular 'colobomata' into three types based on their ophthalmoscopic appearance. The first and commonest type, the pigmented macular 'coloboma,' consists of a circular patch at the macula covered by an irregular mass of pigment, beneath which the choriocapillaris is absent, but small patches of bare sclera and a few choroidal vessels may be seen. There is no scleral ectasia, and normal retinal arterioles pass over the pigmented area, indicating that the main lesion is deep to the inner retinal layers at least. The second type, the non-pigmented 'coloboma,' Mann describes as a round or oval patch at the macula with a white base of bare sclera which is usually ectatic to some extent. There is often pigment clumping at the edge of the lesion, and retinal vessels stop at the margin of the coloboma, suggesting that in this type the retina is also involved. A third, rare, type is represented by those cases in which the macular 'coloboma' is associated with abnormal vessels which may form an anastomosis within the 'coloboma' or run forward from the lesion into the vitreous.[18 19] Not all cases of macular 'colobomata' fall clearly into one of these three groups, and intermediate types do occur. Each of our three cases had macular lesions of the non-pigmented type, and they also do not represent a completely homogeneous group. Mann has speculated that the three types of lesions are caused by a destructive process affecting the developing macular region occurring during the eighth or ninth month, fifth or sixth month, and second or third month of gestation respectively.

The various theories put forward to account for the production of these macular lesions have been reviewed by Mann[1 17] and Sorsby.[2] They fall into two main groups. Firstly, there may be a failure of normal development of the eye, giving rise to the macular abnormality; or, secondly, the development of the eye may be initially normal but later become disorganised by a pathological process, such as infection





Figs. 5a and 5b *Case 2. Both fundi showing the optic disc vessels being dragged temporally towards huge excavated colobomata, which were divided into two 'lobes' by a horizontal band of vessels and pigment.*

in intrauterine life or soon after birth. Although there is no satisfactory explanation for the production of macular 'colobomata' by a failure of development which takes into account both the normal embryological development of the eye and the clinical features of the macular lesions,[2 17] the presence of scleral ectasia and in case 3, the hypoplastic discs may indicate that the causative lesion occurs very early in development.

Most cases with the typical ophthalmoscopic appearance are undoubtedly due to intrauterine infection with *Toxoplasma gondii*. It is also possible that other infective agents may produce similar macular lesions, but this mechanism will not account for the occurrence of macular 'colobomata' in families, and in association with other specific congenital abnormalities. Congenital toxoplasmic chorioretinitis has never been confirmed in siblings and results only from infection of a non-immune mother in pregnancy.[20] Other hereditary macular conditions, such as central areolar pigment epithelial dystrophy[21 22] and progressive bifocal chorioretinal atrophy,[23] may have a similar ophthalmoscopic appearance, but the clinical progression of these conditions in childhood and the absence of scleral ectasia serve to differentiate them from true macular 'colobomata.'

Each of our three patients had a toxoplasma dye test which was negative at 1 in 16 dilution, which makes systemic toxoplasmosis unlikely, since the

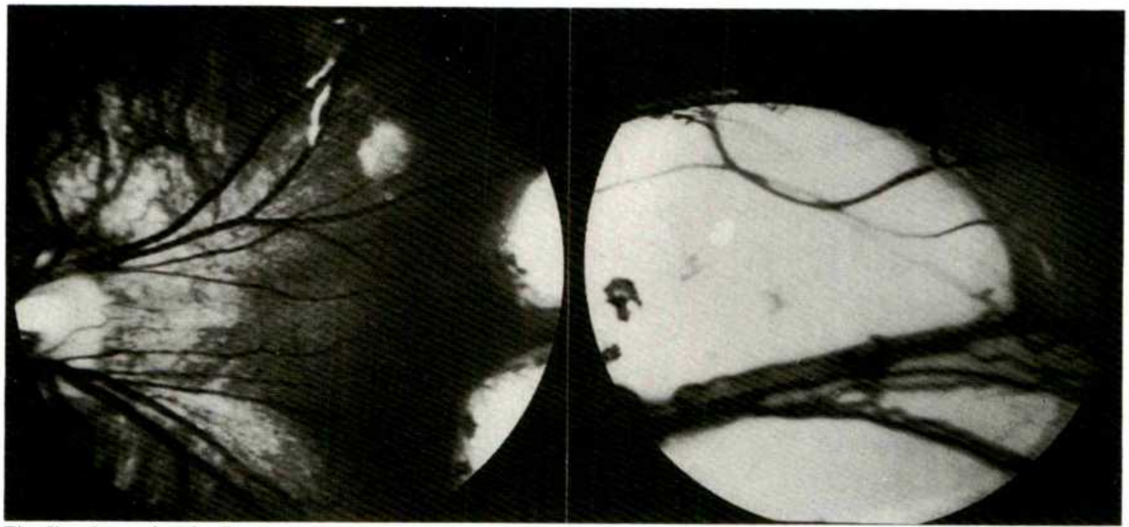


Fig. 5b *Legend under Fig. 5a.*

toxoplasma titre tends to parallel systemic involvement. The serological results do not, however, exclude congenital toxoplasmosis confined to the eye. Zscheile[24] has reported a case of ocular toxoplasmosis confirmed by histopathology in whom the toxoplasma dye test was positive only in undiluted serum. Any toxoplasma titre may be significant in the presence of typical chorioretinal lesions.[25] However, each case reported here had an absent or substantially abnormal electroretinogram, which cannot be explained on the basis of a single macular toxoplasma lesion. The fact that the electroretinogram is abnormal in familial macular 'colobomata' and those occurring as part of a recognisable syndrome points to a developmental origin for the macular lesions in our patients.

Macular dysplasia has been reported in association with several different skeletal abnormalities.[2,4,26]

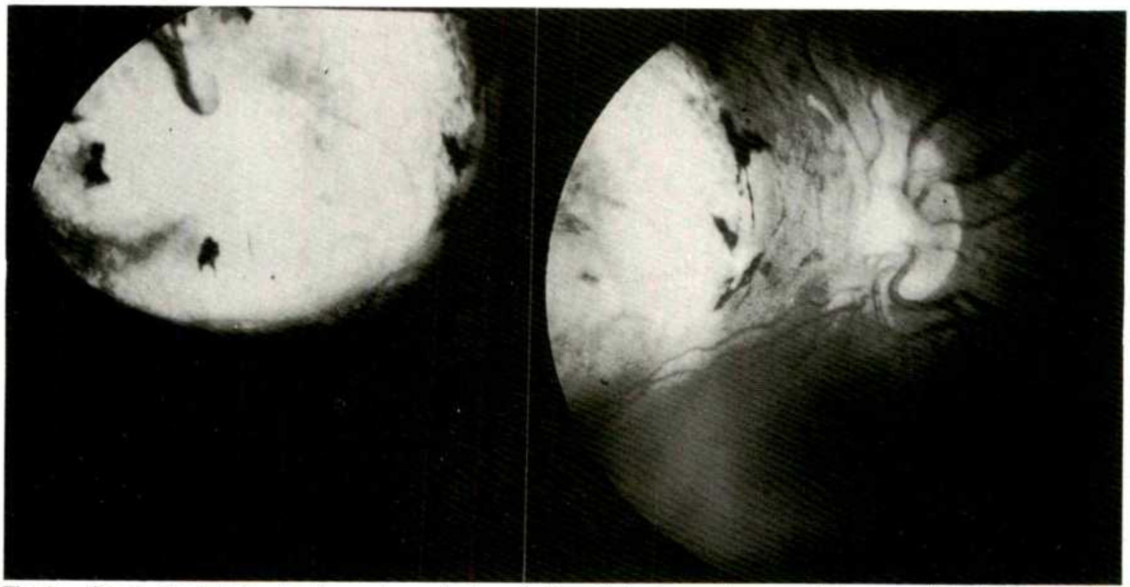


Fig. 6a *Case 3. The right fundus shows a hypoplastic optic disc with the temporal segment being most affected. The macular area is replaced by a circumscribed ectatic area at the base of which was a large choroidal vessel. A thin membrane containing a few spots of pigment covered the coloboma at the level of the retina.*

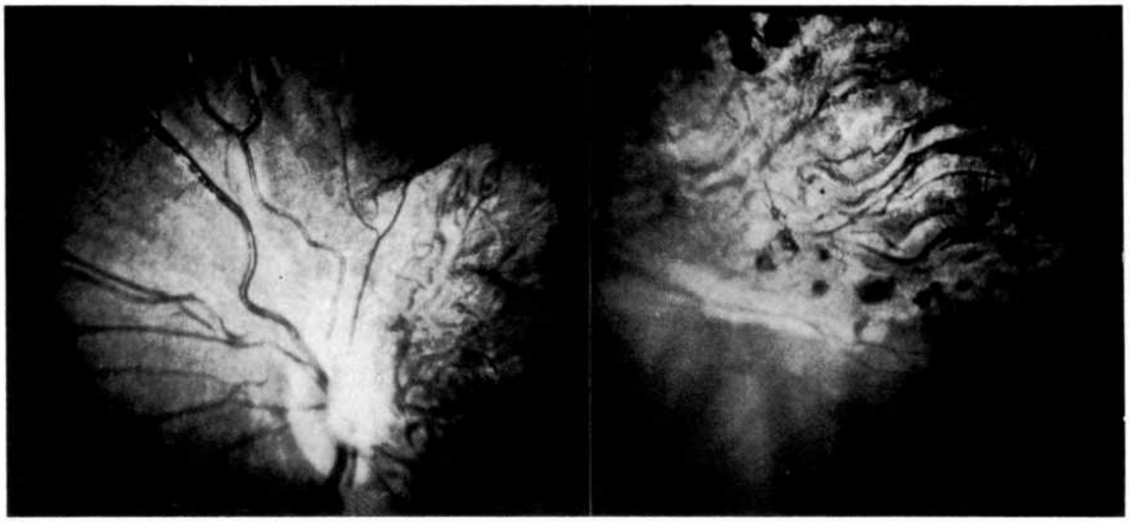


Fig. 6b *Case 3. The left fundus was similar but showed better preserved choroid vessels and pigment, and there was no scleral ectasia.*

Case 1 had skeletal abnormalities consisting of an extra digit but showed none of the other features of apical dystrophy and macular 'colobomata' described by Sorsby.[2] It is interesting that our patient had an extra thumb, as the most constant radiological feature in Sorsby's family was a bifid terminal phalynx of the thumbs and great toes.

The third case reported here had several systemic problems which could not be related to his ocular disease. In addition to the macular lesions both discs were hypoplastic (Fig. 6), the nerve head being especially deficient on the temporal side where the papillomacular bundle normally enters the disc. Optic nerve hypoplasia has not previously been reported in association with macular dysplasia, and the presence of the disc abnormalities suggests that in this case the insult to the developing macular region occurred at an early stage in intrauterine development. The early theories of the pathogenesis of the optic nerve hypoplasia proposed that there is a primary failure of ganglion cell differentiation at the 13–15 mm stage (6 weeks) or their failure to incorporate into the optic stalk at the 19 mm stage (7 weeks).[27] However, the frequent association of optic nerve hypoplasia with central nervous system (CNS) malformations, in particular midline abnormalities such as absent or anomalous septum pellucidum[28 29] or abnormalities of the corpus callosum or with cerebral atrophy[30] and porencephaly,[31] has led to the suggestion that optic nerve hypoplasia may also result from secondary atrophy of the optic nerves during intrauterine development, either as a result of transynaptic degeneration or by a failure of normal cortical induction or influence on optic nerve development.[30] It is also possible that an insult causing a CNS abnormality may also simultaneously damage the developing optic nerve. The optic nerve hypoplasia in our patient may have been related to his CNS abnormality (Fig. 7); optic nerve hypoplasia has been reported in association with colpocephaly.[32] However, the unusual configuration of the hypoplastic discs, with the main defect being related to the deficient papillomacular bundle suggests that the optic nerve hypoplasia in this case is related to the macular dysplasia.

The implications of an abnormal electroretinogram for genetic counselling in a patient with bilateral macular dysplasia is not clear. It is evident

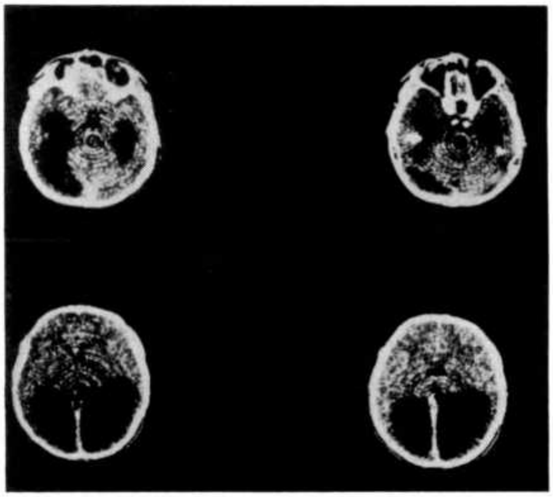


Fig. 7 *Case 3. CT scan showing colpocephaly.*

that patients with bilateral macular dysplasia form a heterogeneous group; macular 'colobomata' (dysplasia) have been reported to have both dominant and recessive modes of inheritance. Dominantly inherited macular 'colobomata' may occur alone[9,10] or with a specific skeletal abnormality[2]; the electroretinogram may be normal[10] or abnormal.[9] An autosomal recessive mode of inheritance is seen with macular 'colobomata' in association with retinitis pigmentosa[15] and Leber's amaurosis[13,14] and is the possible mode of inheritance in 'colobomata' associated with idiopathic infantile hypercalciuria.[11] The two cases reported by Phillips and Stokoe[3] also occurred in siblings. All these patients had absent or severely abnormal electroretinograms. It is difficult to give accurate genetic advice to parents who have had one child with isolated macular 'colobomata' and no family history, especially since the condition may have different aetiologies. If the child has an absent electroretinogram and has had poor vision and nystagmus from infancy, the condition is more likely to resemble Leber's amaurosis in being inherited as an autosomal recessive condition.

Our three cases also illustrate the variability of visual acuity in this condition. Case 1 behaved as a blind child, whereas the other two patients achieved useful vision despite extensive macular lesions and an absent or abnormal electroretinogram. Therefore when a child is seen in infancy with bilateral macular dysplasia it may be better to give the parents a cautiously optimistic visual prognosis, as the vision may later prove to be better than expected from the ophthalmoscopic appearance, though the long term course of the retinal dystrophy is less certain. Indeed Clarke[33] in 1927 described a child with bilateral macular 'colobomata' to whom he gave a 'gloomy' visual prognosis who later went normally through Harrow School, took a degree at Cambridge, and was always good at games, especially tennis. There may be several interpretations of this achievement.

We thank Professor O H Wolff for permission to report details of case 3 and Martin Johns for taking the fundus photographs. Mr A T Moore received financial support from the TFC Frost Charitable Trust.

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Recurrent visual loss in homozygous sickle cell disease

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SUMMARY In sickle cell retinopathy vascular involvement is most frequently recognised at the retinal periphery, but obstruction of perimacular arterioles and of major retinal vessels may also occur. This report describes a patient with homozygous sickle cell (SS) disease with recurrent occlusion of major retinal vessels associated with recurring transient impairment of visual function.

The vaso-occlusive process in sickle cell disease may result in both transient and permanent occlusion of retinal vessels. Although vascular involvement is most frequently recognised at the retinal periphery, obstruction of perimacular arterioles[1,2] and of major retinal vessels[3-6] may also occur. Asdourian *et al.*[1] described remodelling of blood vessels in the perimacular region, which they attributed to arteriolar obstruction, but there was no consistent pattern of associated visual loss. Occlusion of major retinal arterioles in the perimacular region was associated with visual impairment in a patient with sickle cell–haemoglobin C (SC) disease,[6] and the vessels remained non-perfused during the period of observation. The present report describes a patient with homozygous sickle cell (SS) disease with recurrent occlusion of major retinal vessels associated with recurring but transient impairment of visual function.

Case report

This 20-year-old male patient with SS disease attended the sickle cell clinic at the University Hospital of the West Indies. The diagnosis of SS disease was based on standard criteria including a single major haemoglobin band in the position of HbS on alkali and acid haemoglobin electrophoresis, a positive sickling test, and compatible HbA_2 levels.

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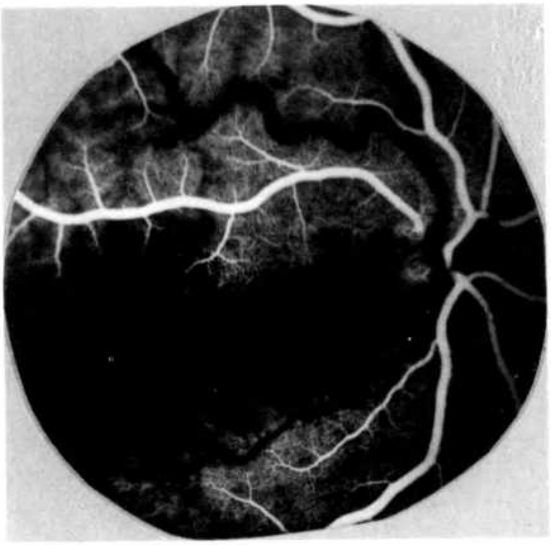

Fig. 1a

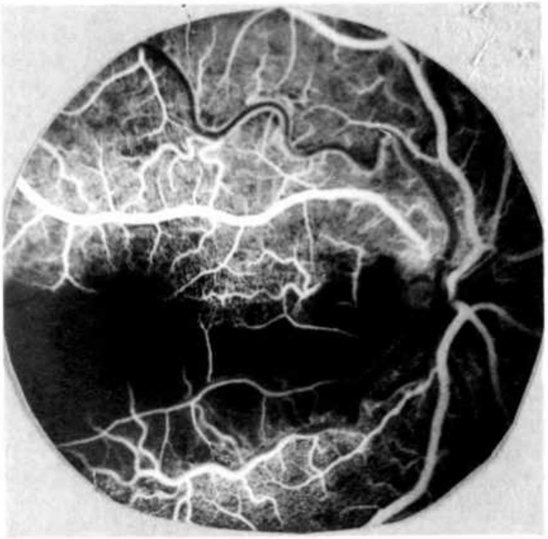

Fig. 1b

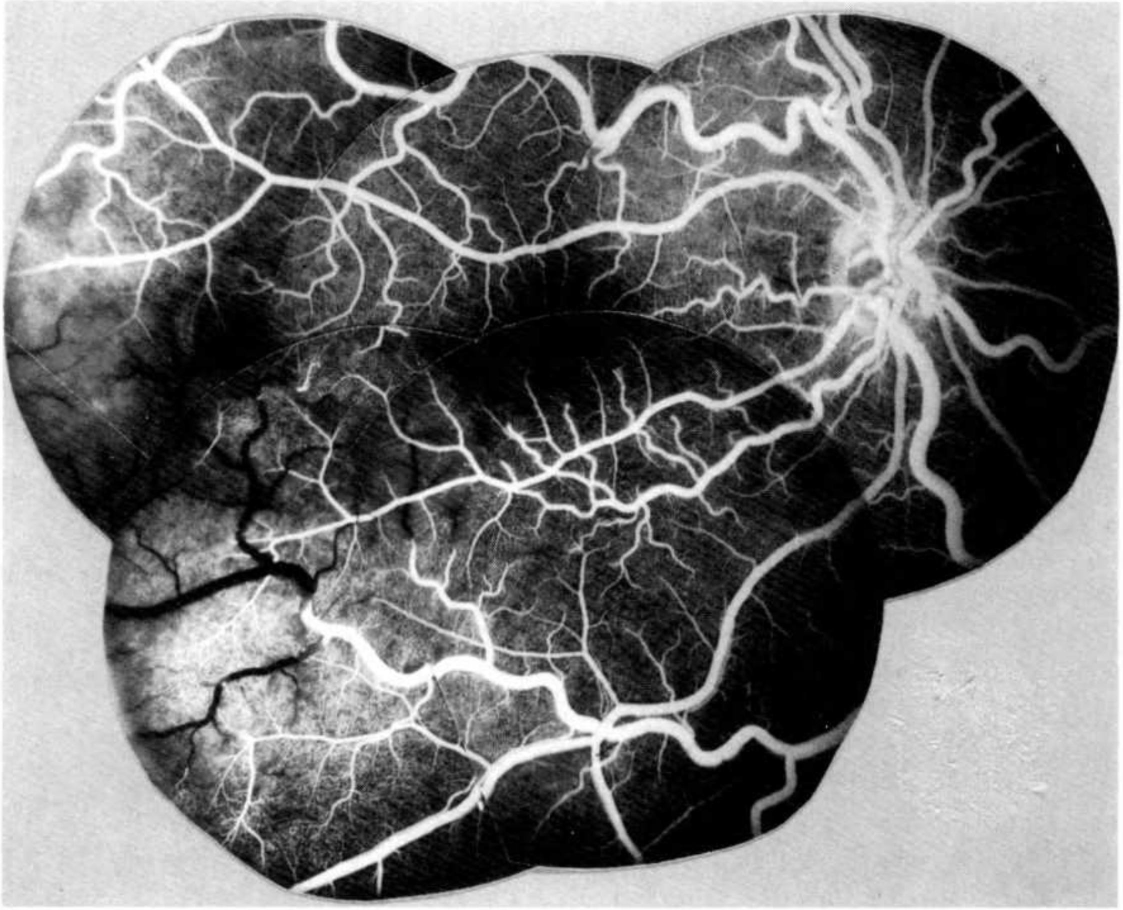

Fig. 1c

Fig. 1 *Fluorescein angiogram of right eye on 21 July 1981.* (a) *Early arterial phase showing non-perfusion of the inferotemporal arteriole from the disc margin and loss of associated capillary perfusion.* (b) *Early venous phase showing retrograde filling of inferotemporal arteriole.* (c) *Late phase showing vessel filling from the optic disc but a non-perfused venous tributary.*

Average steady state haematological values over the past five years were as follows: HbF 4·5%, HbA_2 3·2%, Hb 7·2 g/dl, PCV 19·4%, MCHC 37·8 g/dl, RBC 2·12×10^{12}/l, MCV 91 fl, MCH 33 pg, reticulocytes 13%, Platelets 463×10^{9}/l, irreversibly sickled cells 15%, bilirubin direct reacting 1·2 mg/dl, total 9·4 mg/dl.

On the morning of 21 July 1981 he awoke with a dense central scotoma in the right eye, and the visual acuity was reduced to counting fingers but was normal in the left eye. Ophthalmoscopy revealed the right inferotemporal retinal arteriole to be narrowed, with retinal pallor and a cherry-red (dark) spot at the fovea. Fluorescein angiography confirmed non-perfusion of this vessel from the optic disc in the early arterial phase (Fig. 1a), but the early venous phase showed retrograde filling of this arteriole (Fig. 1b), and the late phase indicated some filling of the arteriole from the optic disc (Fig. 1c). There was a large non-perfused zone in the inferotemporal venous tributary.

Over the next 24 hours visual acuity improved rapidly and was normal two weeks later, though the patient had a small paracentral scotoma. On ophthalmoscopy the inferotemporal arteriole was slightly narrowed, with persistent but less marked retinal pallor, and there was a triangular superficial haemorrhage lateral to the optic disc. The inferotemporal arteriole filled normally on angiography (Fig. 2), and perfusion was restored in branches of the inferotemporal vein, though a perifoveal avascular zone (PAZ) persisted inferolaterally to the macula.

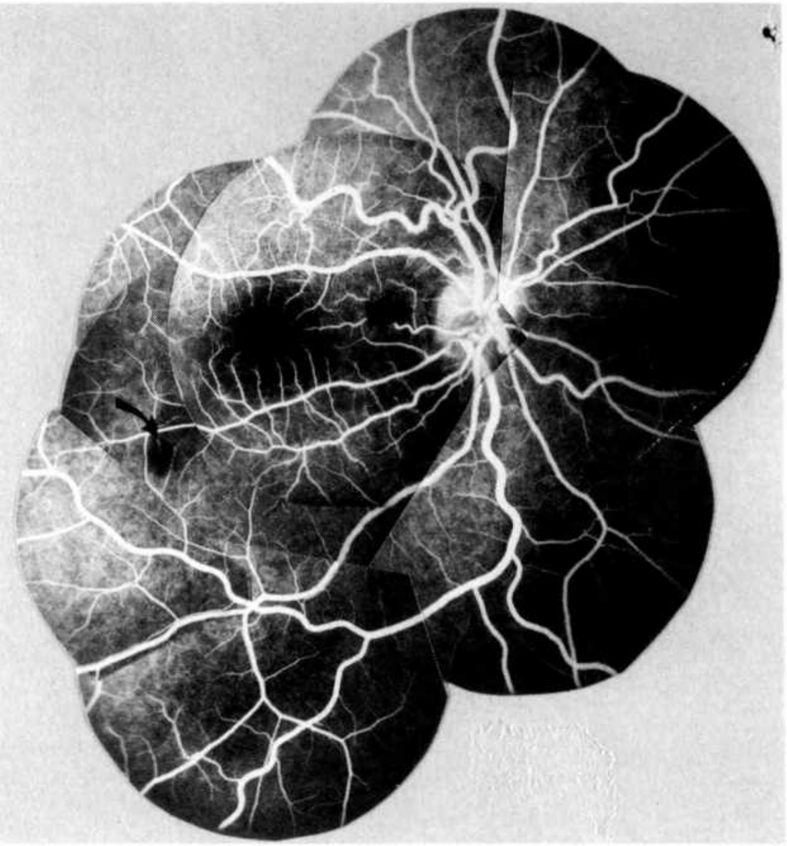

Fig. 2 *Angiogram on 4 August 1981. Perifoveal avascular zone marked by arrow.*

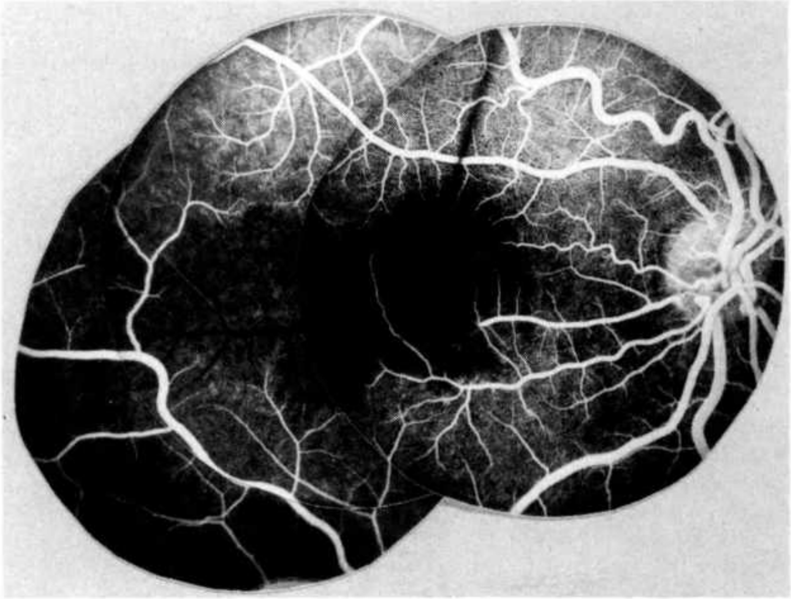

Fig. 3 *Angiogram on 2 February 1982. There is non-perfusion of the inferotemporal retinal arteriole inferior to the macula and loss of associated retinal perfusion.*

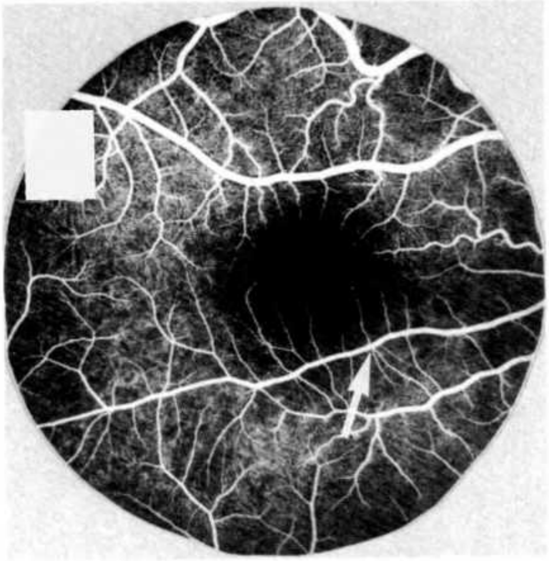

Fig. 4 *Angiogram of same area as in Fig. 3 on 20 September 1982 showing that perfusion has been re-established. Site of previous block indicated by white arrow.*

Seven months after the original episode the patient was asymptomatic, with normal visual acuity, but another obstruction of the inferotemporal retinal arteriole inferior to the macula and a corresponding area of retinal non-perfusion were apparent (Fig. 3). Seven months later he was asymptomatic, with normal visual acuity, and angiography showed normal filling of the inferotemporal retinal arteriole and remodelling of the perifoveal capillary network (Fig. 4). Eighteen months after the original episode, and while working exposed in cold weather at 4000 feet (1220 m), he lost vision in the right eye. On examination the visual acuity was 6/24, and there was cloudy swelling in the macular area with cotton wool spots at the posterior pole. Angiography revealed non-perfusion of branches of the supero- and inferotemporal retinal arterioles distal to the macula, with corresponding areas of capillary non-perfusion (Fig. 5). On the next day some flow had returned, though there was persistent non-perfusion of a major branch of the superotemporal retinal arteriole and of a minor branch of the inferotemporal arteriole (Fig. 6). One week later visual acuity was normal, though the affected branch of the superotemporal vessel remained non-perfused (Fig. 7). Three weeks later angiography indicated occlusion of a major branch of the superotemporal vessel at a more distal site, and there was evidence of collateral circulation from more temporal peripheral vessels, though the block in the branch of the inferotemporal arteriole had resolved (Fig. 8).

Discussion

Occlusion of the central retinal artery or its major branches in sickle cell disease may occur spontaneously[3-5] or following retrobulbar anaesthesia.[7,8] The remodelling of the perimacular vasculature that attends occlusion of smaller arterial branches has

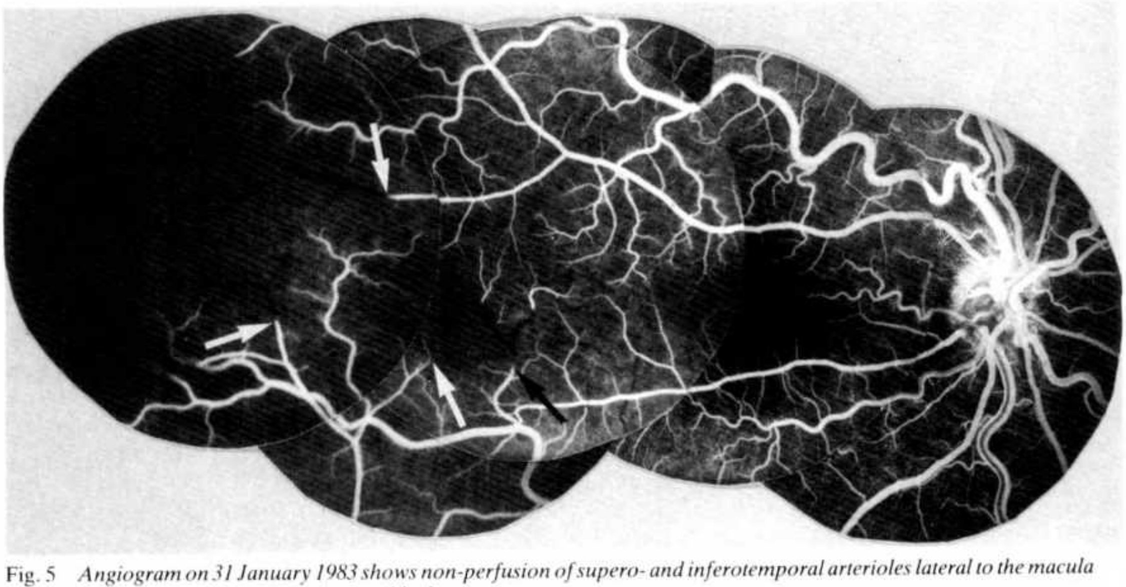

Fig. 5 *Angiogram on 31 January 1983 shows non-perfusion of supero- and inferotemporal arterioles lateral to the macula (white arrows) and venous non-perfusion (black arrow).*

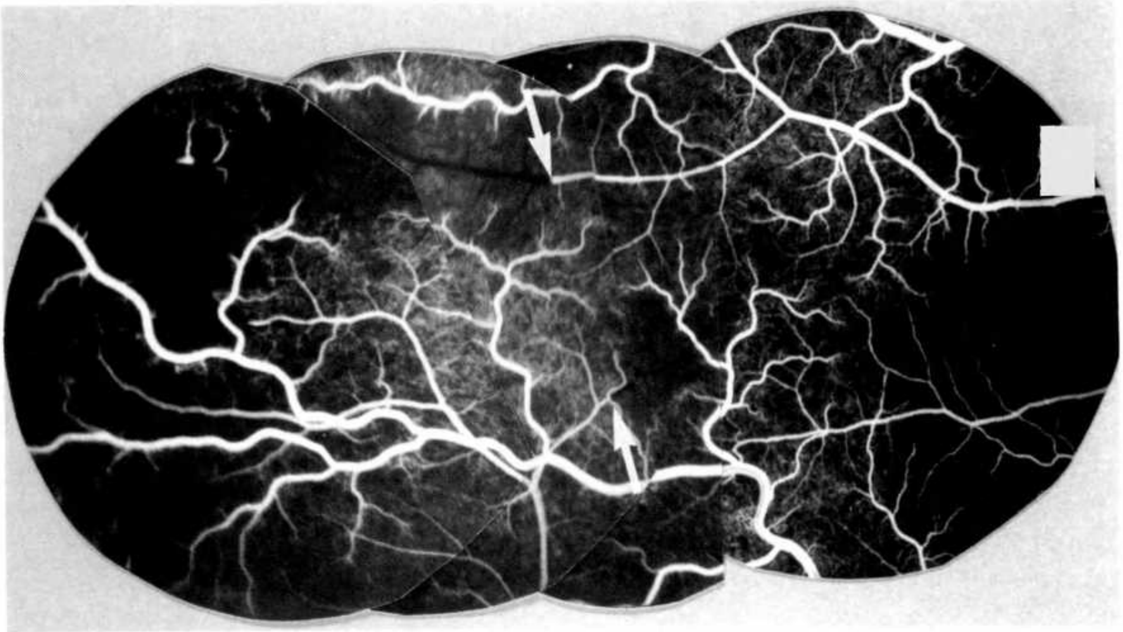

Fig. 6 *Angiogram on 1 February 1983 shows that only two sites of arterial non-perfusion (white arrows) persist.*

been well reviewed.[1] The precipitating factors for such occlusive episodes are unknown, though the simultaneous involvement of multiple sites suggested to Chopdar[6] that the probable mechanism was embolism from sickling elsewhere in the body.

The frequency of such occlusive episodes is unknown, as small branch arteriolar occlusion in the perimacular area may be asymptomatic,[1] though occlusions of larger branches are generally associated with visual symptoms. The observation that this was the only patient with such symptoms among a group of approximately 800 adults with SS disease and 300 adults with SC disease suggests that this is an unusual occurrence. The reasons for the arterial occlusions in this patient are unclear. Most haematological indices were within the normal range for patients with SS

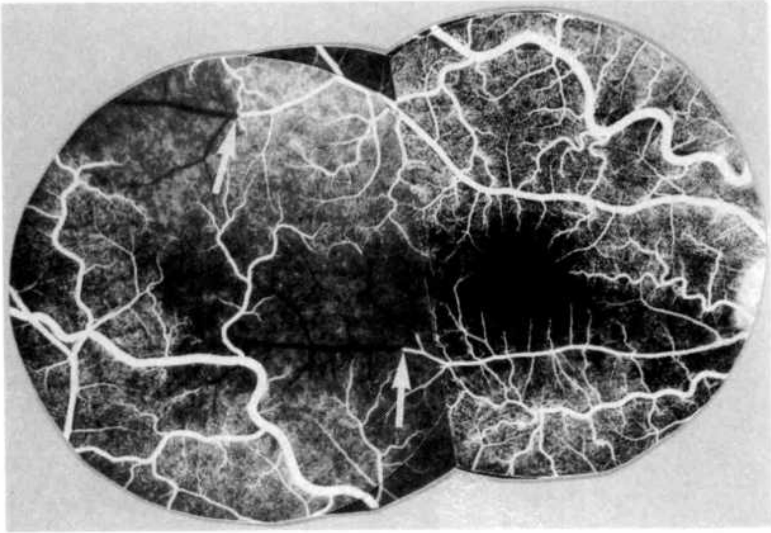

Fig. 7 *Angiogram on 8 Februrary 1983 shows non-perfusion of the superotemporal arteriole more proximally (upper arrow) than in the previous week and a new block of inferotemporal arteriole (lower arrow).*

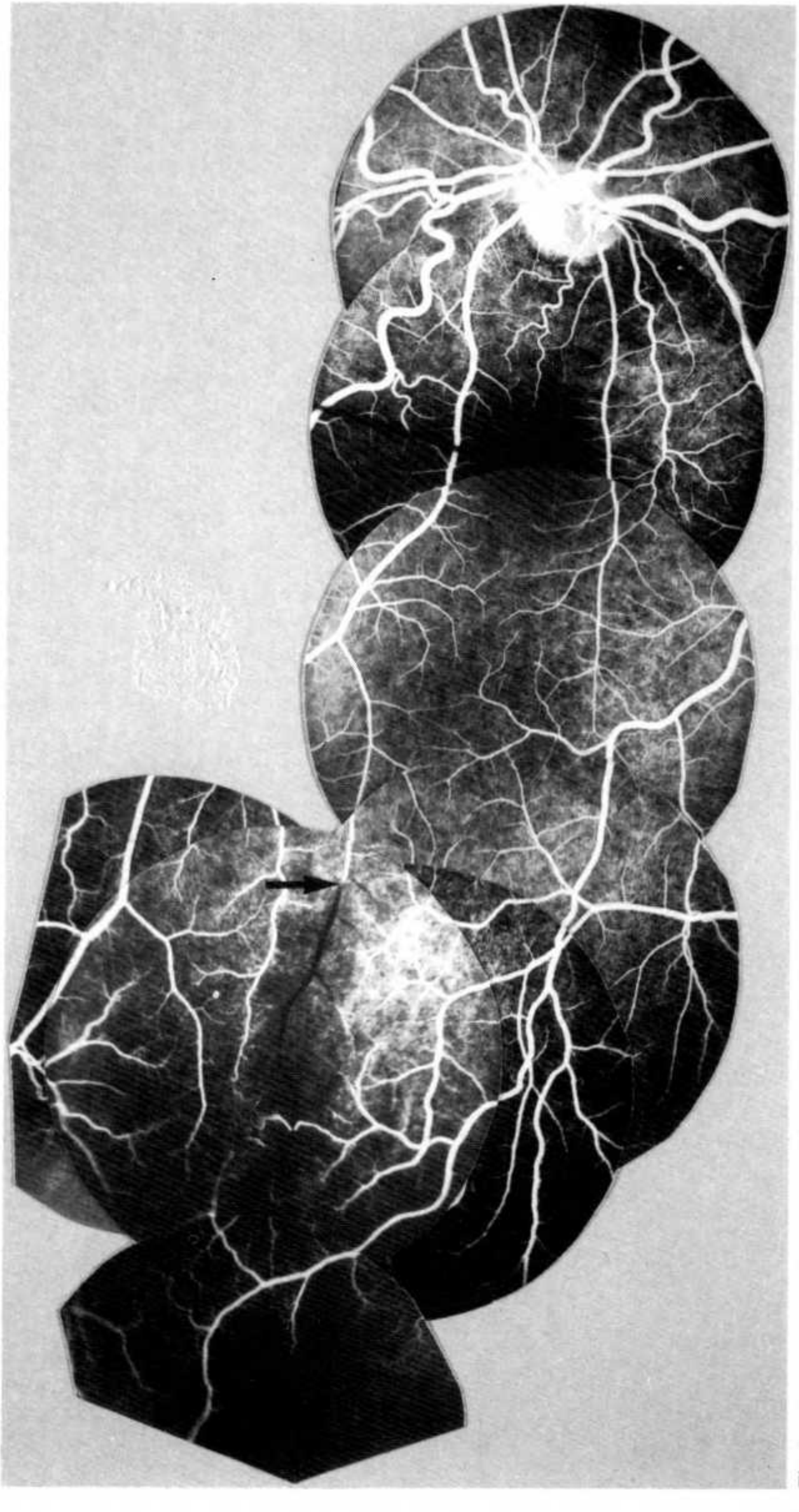

Fig. 8 *Angiogram on 1 March 1983 indicates non-perfusion of the superotemporal arteriole at the more distal site (black arrow) and that the block of inferotemporal vessel has resolved.*

disease of the same sex and age,[9] though the MCHC was close to the 95th percentile and the total bilirubin level above it. The mean cell haemoglobin concentration, computed from the centrifuged haematocrit, was 39 g/dl on the day of the original episode, raising the possibility that cells of a high internal viscosity and consequently lowered deformability had compromised the retinal circulation. It is well recognised that the red cells in patients with SS disease are markedly heterogenous, and there is increasing interest in the pathological significance of the dense cell fraction. Although direct measurements of dense cells are not available in this patient, the high MCHC indirectly indicates an increased dense cell fraction. There were no obvious precipitating factors of the initial episode, but the second symptomatic episode occurred while the patient was working at altitude under cold conditions, both factors known to favour sickling.

Vessel involvement at the posterior pole in sickle cell disease presents a spectrum ranging from central retinal artery occlusion, major branch occlusion, minor branch occlusion, to perimacular capillary drop-out and formation of perifoveal avascular zones. The last are frequently asymptomatic and without reduced visual acuity,[10] and impairment of vision generally becomes more marked with involvement of the larger vessels. The present case illustrates the transient nature of some occlusions of larger vessels in sickle cell disease, and this condition should be recognised as a cause of transient or intermittent visual loss.

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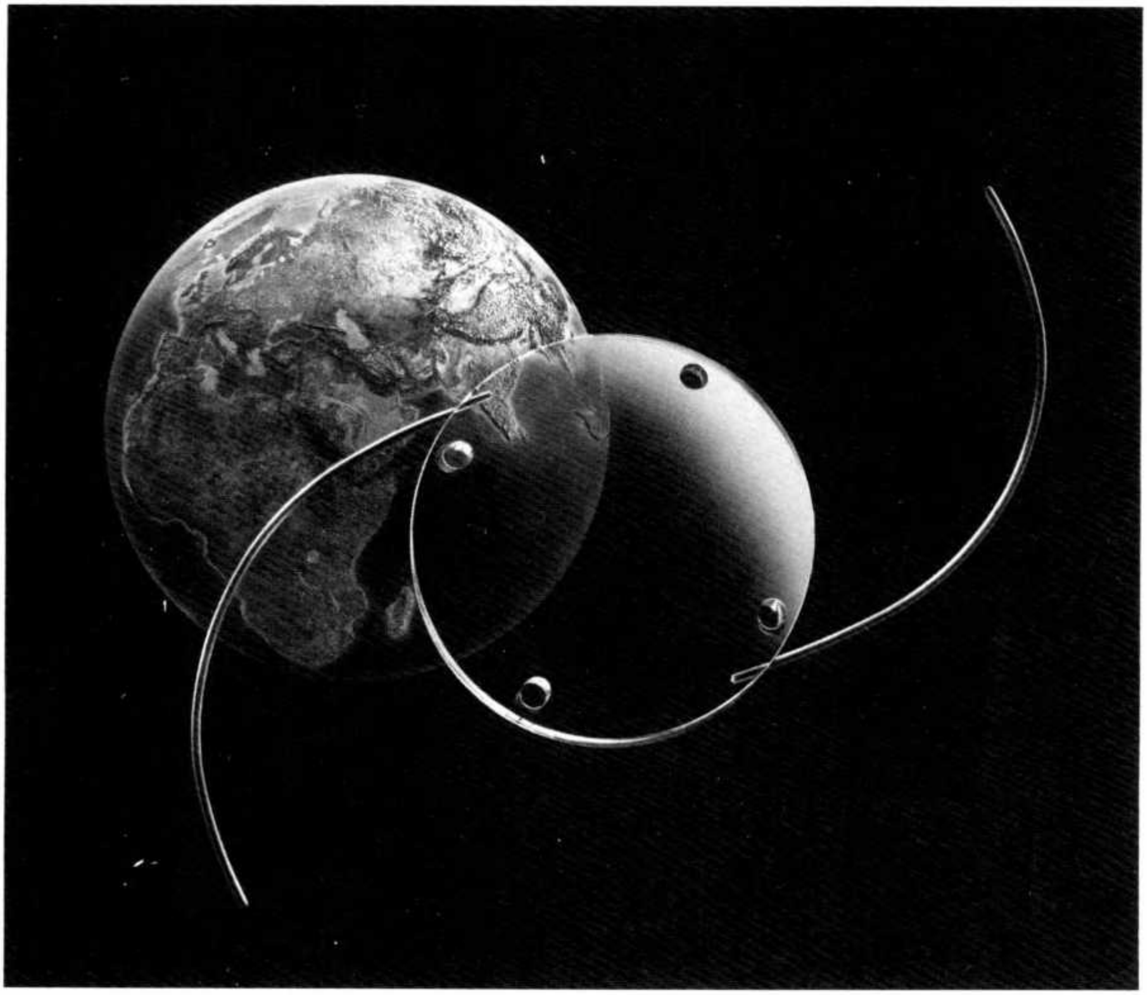

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Serum complement components in patients with trachoma

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SUMMARY Serum C1q, C3, C4, and C5 components of complement levels were measured in 56 healthy subjects and 98 patients with trachoma. Serum C1q and C3 levels were found to be significantly low in stages II and III. There was no change in serum C4 and C5 levels in any of the stages. The levels of C1q and C3 complement components in serum in stages II and III returned to normal as the disease resolved following the medical treatment.

Trachoma is estimated to be responsible for 5% of visual impairment and blindness in India.[1] Certain features of this disease have led to a suggestion that immunological responses may play some part in its pathogenesis.[2] The complement system has a role in defending the host against infection.[3] It has been established that activated complement is an important mediator of tissue inflammation.[4] The ocular tissue is known to contain components for both classical and alternate pathway of activation of complement.[5] However, very little work is available on serum complements in ocular diseases. In one report it has been found to be altered in acute adenovirus conjunctivitis.[6] Here we report observations on the levels of complement components in serum in patients with different stages of trachoma and the effects of medical treatment.

Material and methods

The study was carried out on 56 healthy subjects and 98 patients with trachoma attending the outpatient department of Guru Nanak Eye Centre, New Delhi. The control group comprised healthy subjects who had no evidence of any ocular or systemic disease and who attended the Eye Centre during the same period mainly for the purpose of refraction. The patients with trachoma did not have any other ocular or systemic disease. The age and sex distribution of healthy subjects and the trachoma patients are given in Table 1.

The diagnosis of trachoma was established by detailed clinical examination with the help of a slit-lamp biomicroscope and the stages were determined in accordance with MacCallan's classification[7] as modified by the World Health Organisation.[8] The diagnosis of trachoma was further confirmed in the laboratory by Giemsa staining of inclusions in conjunctival scrapings. Only the Giemsa-positive cases were included in this study.

The serum samples were stored at −20°C and assayed within three to four days of collection. They were analysed for C1q, C3, C4, and C5 complement components by a single radial immunodiffusion technique.[9] Monospecific goat antisera against human C3, C4, and C5 complement components and their respective reference standards were obtained from Meloy Laboratories, Virginia, USA. Antihuman C1q complement component serum was obtained from Behring Institute, Frankfurt, West Germany. The levels of C1q complement component in the samples of sera were compared with WHO reference standard serum 67/97 and expressed in units/dl, the WHO reference standard being taken as 100 units/dl.

Patients with trachoma stages I, II, and III were treated by oral sulphonamides (sulphamethoxazole 30 mg per kg of body weight daily in divided doses for adults and proportionately less for children according to body weight) for three weeks and topical therapy with tetracycline ointment 1% twice daily for 90 consecutive days. They were followed up once a week to ensure compliance with the treatment. On every visit a thorough clinical examination with the help of a slit-lamp biomicroscope was done. The treatment was considered to be effective when resolu-

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Table 1 *Age and sex distribution of healthy subjects and patients with trachoma*

	M	*F*	*Total*	*Age in years*				
				20 and under	*21–30*	*31–40*	*41–50*	*51 and over*
Healthy subjects	35	21	56	20	24	8	4	–
Trachoma patients	51	47	98	34	23	18	17	6
Stage I	12	14	26	17	8	1	–	–
Stage II	13	11	24	14	7	3	–	–
Stage III	15	10	25	3	6	7	7	2
Stage IV	11	12	23	–	2	7	10	4

M=males F=females

tion of the disease was noted clinically and also Giemsa staining became negative for inclusions in conjunctival scrapings. Sixty-two patients fulfilled these criteria for effective medical treatment, and from them serum samples were again collected four months after the resolution of the disease as a result of medical treatment.

Stage IV being the remission stage of the disease required no medical treatment.

Results

Serum C1q, C3, C4, and C5 complement component levels in healthy subjects and patients with trachoma are given in Table 2. The statistical analysis of the results was done by Student's *t* test and $p<0{\cdot}05$ was considered to be statistically significant. It was observed that the levels of serum C1q and C3 complement components were significantly lower than those in healthy subjects ($p<0{\cdot}05$ and $p<0{\cdot}01$ respectively). However, there was no statistically significant difference in the levels of serum C4 and C5 complement components.

Table 2 also shows the levels of C1q, C3, C4, and C5 complement components in stages I, II, III, and IV of trachoma. The serum C1q complement component level was significantly lower in stage II ($p<0{\cdot}05$) and stage III ($p<0{\cdot}02$) than were the respective levels in healthy subjects. The serum C3 complement component level was also lower in stage II ($p<0{\cdot}02$) and stage III ($p<0{\cdot}01$). However, the levels of serum C4 and C5 complement components were the same in all stages as in healthy subjects.

Table 3 shows the serum C1q, C3, and C4, and C5 complement component levels in patients with trachoma after the resolution of the disease following medical treatment. There was a significant rise in serum C1q complement component level ($p<0{\cdot}001$) and C3 complement component level ($p<0{\cdot}001$) in treated patients (stages I+II+III), and the levels almost attained those found in the healthy subjects. However, there was no significant alteration in the serum C4 and C5 complement component levels in these stages. Of the different stages of trachoma, only in stages II and III was there a significant rise in C1q level ($p<0{\cdot}001$ and $p<0{\cdot}01$ respectively) and C3 level ($p<0{\cdot}01$ and $p<0{\cdot}02$ respectively); the changes in the level of serum complement components C1q,

Table 2 *Serum complement components (C3, C4, and C5) levels mg/dl and C1q in units/dl in patients with different stages of trachoma and their correlation with the levels in healthy subjects*

	No. of cases	*C1q Mean ± SD*	*C3 Mean ± SD*	*C4 Mean ± SD*	*C5 Mean ± SD*
Healthy subjects	56	129·2±36·4	169·2±47·5	34·4±17·0	11·8±6·5
Trachoma patients (all stages)	98	116·8±29·5 ($p<0{\cdot}05$)	148·8±32·1 ($p<0{\cdot}01$)	31·0±14·0 (NS)	10·6±6·1 (NS)
Stage I	26	121·6±34·3 (NS)	157·4±32·0 (NS)	32·0±15·7 (NS)	11·2±6·1 (NS)
Stage II	24	113·2±21·1 ($p<0{\cdot}05$)	141·8±29·3 ($p<0{\cdot}02$)	30·8±13·6 (NS)	10·1±5·7 (NS)
Stage III	25	108·5±25·5 ($p<0{\cdot}02$)	135·8±31·7 ($p<0{\cdot}01$)	29·5±14·1 (NS)	9·9±6·4 (NS)
Stage IV	23	123·1±34·1 (NS)	161·4±29·5 (NS)	31·6±12·9 (NS)	11·3±6·5 (NS)

NS=not significant statistically.

Table 3 *Serum complement components (C3, C4, and C5) in mg/dl and C1q in units/dl in stage I, II, and III of trachoma after treatment and their correlation with pretreatment levels*

Stages	*No. of cases*	*C1q Mean ± SD*	*C3 Mean ± SD*	*C4 Mean ± SD*	*C5 Mean ± SD*
Stages I + II + III					
Pretreatment	75	114·9±27·9	145·2±32·2	30·8±14·4	10·4±6·0
Post-treatment	62	130·8±25·1	162·2±25·6	32·9±13·9	11·4±5·8
p Value		($p<0·001$)	($p<0·001$)	(NS)	(NS)
Stage I					
Pretreatment	26	121·6±34·3	157·4±32·0	32·0±15·7	11·2±6·1
Post-treatment	22	124·8±27·4	162·0±28·4	32·9±13·9	11·5±5·8
p Value		(NS)	(NS)	(NS)	(NS)
Stage II					
Pretreatment	24	113·2±21·1	141·8±29·3	30·8±13·6	10·1±5·7
Post-treatment	20	137·0±21·9	165·8±23·0	33·7±12·9	11·7±6·3
p Value		($p<0·001$)	($p<0·01$)	(NS)	(NS)
Stage III					
Pretreatment	25	108·5±25·5	135·8±31·7	29·5±14·1	9·9±6·4
Post-treatment	20	130·9±26·0	158·9±25·7	32·2±12·1	10·9±5·5
p Value		($p<0·01$)	($p<0·02$)	(NS)	(NS)

No medical treatment was given in stage IV because this was the remission stage of the disease.

C3, C4 and C5 in stage I, and C4 and C5 in stages II and III were not statistically significant.

Discussion

The presence of a multiple-system mediating host defence makes the evaluation of the specific role of any single system difficult. This has been particularly true in assessing the role of complement in ocular diseases. In spite of such difficulties it is apparent that complement does have a specific role in the host's defence in man.[10] The complement system in human serum is able to neutralise or enhance neutralisation of certain viruses in vitro by mechanisms involving both the classical and alternate pathway.[11 12] Diseases associated with altered serum complement levels in man have been observed during hepatitis type B, Epstein-Barr virus infection, Argentine haemorrhagic fever, and subacute sclerosing panencephalitis.[13] It has been shown in corneal inflammation that activation of complements by either the classic or the alternate pathway may be involved.[14 15]

C1q, C3, and C4 components of complement represent acute-phase reactant in human serum.[16] C3 component of complement is common to both the classical and the alternate pathways of activation and is biologically important in that its activation products mediate many of the features of the inflammatory response.[17] The serum concentration of C3 complement component is therefore expected to be affected by accelerated catabolism as a result of complement activation. A low serum concentration of C3 component in serum has been reported in patients with acute adenovirus conjunctivitis,[6] acute viral lower respiratory tract illness,[18] Argentine haemorrhagic fever,[19] and acute type B hepatitis.[20] In the present study significantly low levels of C3 complement in serum have been observed in patients with stages II and III of trachoma. Viral lysis initiation is reported to be carried out by C1q component of complement.[10] A significant depression of serum C1q component of complement level in patients with stages II and III of trachoma has been observed in the present study. C1q complement component in serum has also been reported to be low in acute adenovirus conjunctivitis[6] and Junin virus haemorrhagic fever.[19] Low levels of C1q and C3 complement components in serum may be due to the activation of the classical and/or alternate pathway, transient depression of complement component synthesis, increased catabolism, or the presence of inhibitors of complement action.

There was no significant alteration in the levels of C4 and C5 complement components in serum in any of the stages of trachoma. In acute adenovirus conjunctivitis also no significant alterations in C4 and C5 levels in serum have been reported.[6]

C1q, C3, and C4 components of complement in serum were normal or increased during the acute phase and normal in the convalescent phase in patients with Epstein-Barr virus infection.[21] It has been suggested that complement is important to the patients recovery from viral respiratory tract infection.[22] The observation that the low levels of C1q and C3 complement components became normal when the disease resolved spontaneously, as in stage IV, or after treatment, as in stage II and III, is therefore interesting.

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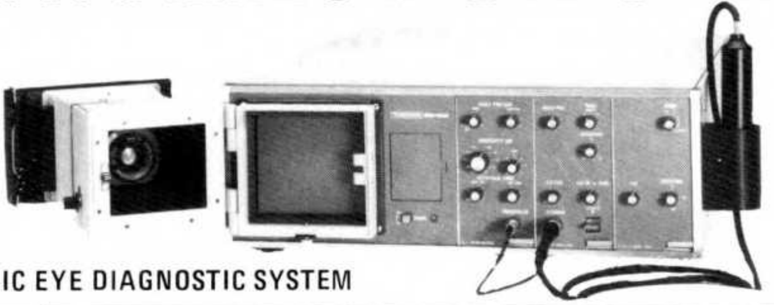

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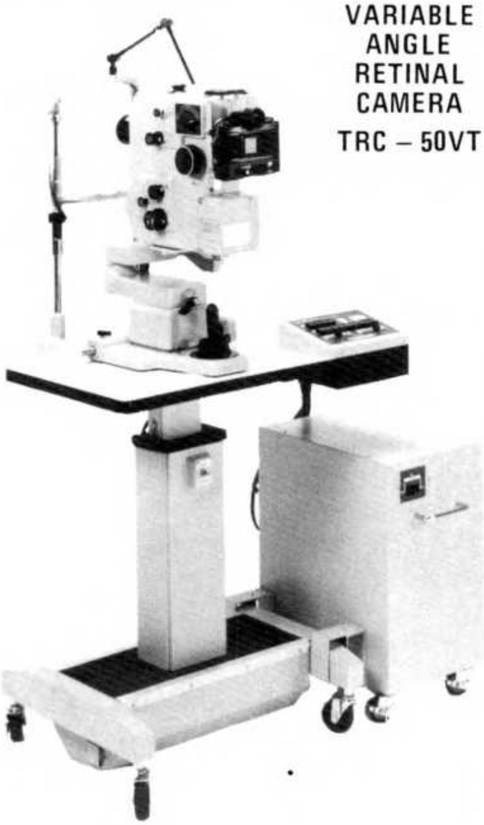

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British Journal of Ophthalmology, 1985, **69**, 711–713

Congenital fistulae of the lacrimal gland

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SUMMARY A 15-year-old female was found on routine clinical examination to have bilateral asymptomatic congenital fistulae of the lacrimal glands. The fistulae opened into the conjunctival sac at the external canthus of both eyes. Temporary occlusion of these openings produced an immediate and significant reduction in tear secretion in both eyes.

Congenital fistulae of the lacrimal gland are rarely reported. Since their original description by Beer[1] 16 cases have been recorded in the literature, only one of which was bilateral.[2]

Case report

A 15-year-old female presented in November 1983 with a three-week history of itchy, discharging eyes. Her symptoms had failed to respond to topical chloramphenicol drops prescribed by her family doctor. The patient had no previous ocular complaints but gave a history of hay fever and had suffered from eczema as an infant. Visual acuity was 6/6 unaided right and left, and the eyes were structurally sound apart from a mild bilateral follicular conjunctivitis with associated mucopurulent discharge. Conjunctival swabs from both eyes were bacteriologically sterile. Cytological examination of scrapings from the lower tarsal conjunctiva of each eye showed a mixed infiltrate of neutrophils, lymphocytes, and eosinophils; inclusion bodies were absent. On the basis of these findings a diagnosis of allergic conjunctivitis was made, and the patient was treated with topical betamethasone 0·1% drops three times daily to both eyes.

Ten days later the patient was asymptomatic, and signs of conjunctival inflammation were less. Examination on this occasion revealed a small opening on the conjunctival aspect of the external canthus of the right eye, and a similar opening was present at the external canthus of the left eye (Fig. 1). When the eyelids were held apart and drawn away from contact with the globes, a small amount of clear fluid was seen to discharge from each orifice on to the skin at the external canthi. A 0·5 mm lacrimal probe was passed without difficulty for a distance of approximately 8 mm from the right orifice and for a distance of almost 10 mm from the left orifice. A roentgenogram taken after injection of contrast medium into both of these openings clearly demonstrated the presence of a fistula extending upwards towards the lacrimal gland on each side (Fig. 2). There was no clinical abnormality of the lacrimal glands, and the lacrimal passages on both sides were normal. A Schirmer 1 test showed greater than 20 mm of wetting in both eyes after five minutes. However, after occlusion of each orifice for 10 minutes with a silicone rod of 0·7 mm diameter a repeat Schirmer 1 test showed only 11 mm of wetting in the right eye and 7 mm in the left eye. The silicone rods were then removed, and 10 minutes later the Schirmer 1 test showed wetting of 22 mm in the right eye and 18 mm in the left. This sequence was repeated on two occasions with similar results.

The patient had no other ocular or systemic congenital abnormalities. Examination of other family members including both parents, five siblings, and the maternal grandparents was negative.

Discussion

Congenital fistula of the lacrimal gland is a rare anomaly. Blanksma and van de Pol[2] reviewed the literature and found 13 cases of unilateral fistulae to which they added the first recorded case of a bilateral occurrence. We are aware of two additional reports,[3][4] both of which describe unilateral fistulae.

Patients with congenital fistula of the lacrimal gland commonly present with epiphora[3-6] or with a purulent discharge from a fistula which has undergone cystic dilatation with secondary infection.[2] It is

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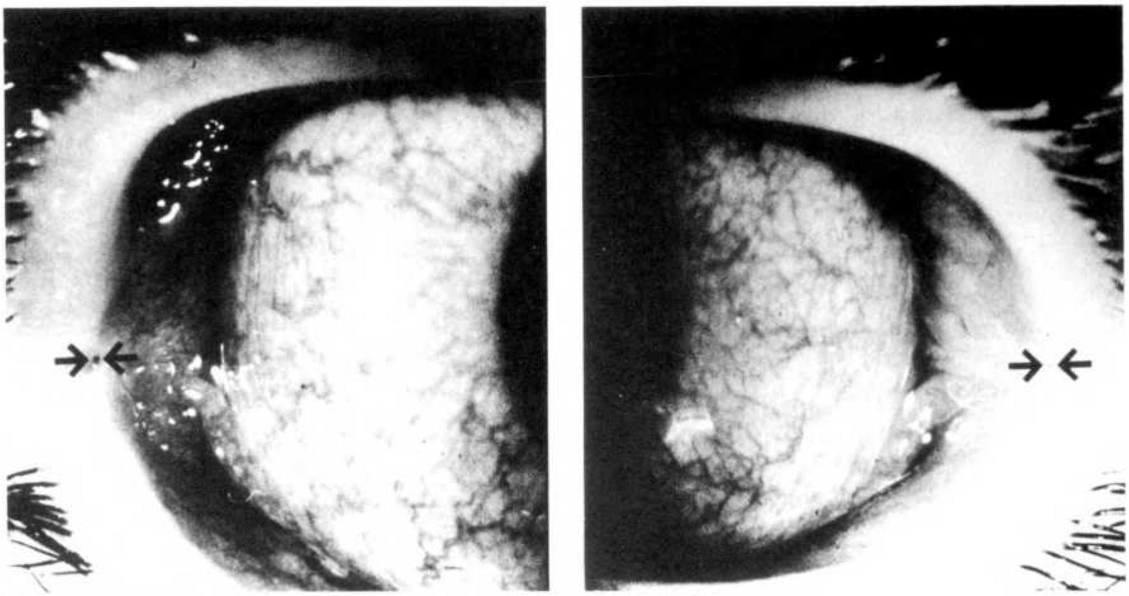

Fig. 1a *Right eye.*

Fig. 1b *Left eye.*

Figs. 1a b *The external canthi of both eyes showing the orifices of the lacrimal gland fistulas (arrows).*

interesting that in spite of the congenital nature of these fistulae the clinical presentation is often delayed for many years after birth.[2,8] This is probably related to the effect of evaporation on the discharge, which is often small in amount and intermittent in nature.[10] In the present case the patient gave no history of epiphora, and discovery of the fistulae was accidental during routine clinical examination. This is not surprising, since each fistula opened into the conjunctival sac at the external canthus, so that the discharge from these openings merged with the tear film. Our patient will probably remain asymptomatic unless one of the fistulae becomes infected, as occurred in the case reported by Blanksma and van de Pol[2] in which bilateral fistulae had remained asymptomatic for 35 years and the orifices of the fistulae were similar in location to those in the present case.

Although the discharge of tears from fistulae of the lacrimal gland is usually slight, an interesting feature in our patient was the finding that temporary occlusion of the orifices repeatedly produced a significant reduction of 50% or greater in tear secretion in both eyes as determined by the Schirmer 1 test. Putterman[3]

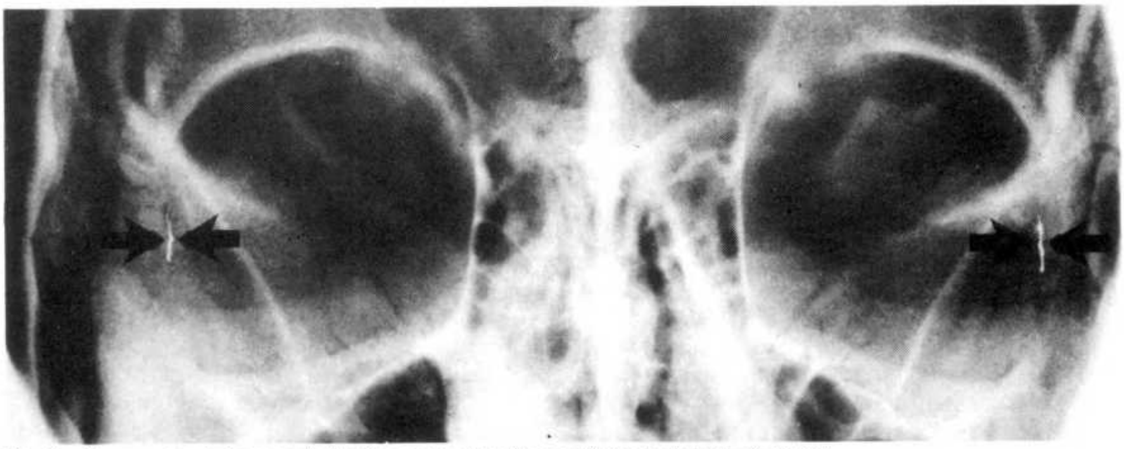

Fig. 2 *X-ray contrast photograph showing contrast medium outlining both fistulas (arrows).*

found an increase in tear secretion of similar magnitude following transplantation of a fistula of the lacrimal gland from the external eyelid to the conjunctival sac. Our finding leads us to suggest that the fistulae in the present case may represent true lacrimal ductules which are aberrant in position. Desai[9] points out that, while the majority of the lacrimal ductules normally open into the temporal part of the superior fornix, a larger ductule called the inferolateral duct traverses the lateral portion of the gland and, passing deep to the conjunctival epithelium, opens below and lateral to the main openings. We believe that the fistulae in the present case represent an anomaly in which during development of the inferolateral ducts the latter open into the conjunctival sac at a lower level than normal.

The finding that the fistulae in this case contribute significantly to the overall tear secretion in both eyes will be an important consideration should the question of surgery arise. In that event the approach suggested by Putterman,[3] Terlinck,[5] and Malhotra,[7] in which the fistula is transplanted into the upper conjunctival fornix, would be the treatment of choice rather than the alternative method used by Blanksma and van de Pol[2] and by Ling,[8] in which the fistula along with an adjoining portion of lacrimal gland is completely excised.

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Book reviews

Your Eyes and Their Care. By MONTAGUE RUBEN AND JUSTIN WINTLE. Pp. 144. £3·95. Granada: London. 1985.

The book is a joint offering by a contact lens wearing journalist and a medical contact lens specialist However, it covers not only contact lenses but the whole field of ophthalmology for the benefit of the laymen.

One would hope that a book of this type would give helpful advice and dispel some of the myths about so-called 'eye care.' Unfortunately one is in for a disappointment here· on page 2, for example, we are told that 'television screens, artificial lighting, abundant reading materials . can all contribute to individual cases of deteriorated vision.' One suspects that J Wintle (the journalist) must have slipped this in without M Ruben (the ophthalmologist) noticing

Chapters 1 and 2 describe the structure and optical characteristics of the eye quite nicely, but we are in for another shock in chapter 3 when the old chestnut of myopia acquired by too much reading is presented once again. One feels that, although this is a book for laymen, nevertheless such an inflammatory statement as 'children who read too much, or read in circumstances where they have constantly to "strain" the eyes, are likely to increase the physical length of the eye artificially, and, as we saw in the last chapter, this is the main cause of short sight' ought to be backed up by proper evidence.

The chapter on contact lenses and their problems is, as one would expect, excellent and pulls no punches in describing complications

Chapters on glaucoma, corneal degeneration, lids and tears, squint, cataract, retina, uvea, trauma, and blindness are satisfactory, but there is a strange chapter on 'eye strain.' The disorder is not defined (which is not surprising as it probably does not exist), and, having told the reader that it may be caused by long or short sightedness and astigmatism, the text drifts away from the subject into a desultory series of observations about 'off the shelf' spectacles, ocular dominance, amblyopia, and the examination of children.

The book is of little interest to ophthalmologists but would possibly attract a readership of moderately well educated laymen. REDMOND J H SMITH

Ophthalmology. 3rd edn. By KENNETH WYBAR AND MALCOLM KERR MUIR. Pp. 375. £7·95. Bailliere Tindall: London. 1984.

This third edition of what has become one of the standard postgraduate ophthalmology texts has been significantly changed and brought up to date to good effect. With the help of coauthor Malcolm Kerr Muir, Kenneth Wybar's original text has been rewritten, in particular in the advancing topics of retinal disease, surgery of the vitreous, immunology, and investigative ophthalmology. It is pleasing to see CT scanning and nuclear magnetic resonance receiving proper emphasis, especially in the investigation of orbital disease.

The book takes the traditional form of describing disease under the usual anatomical headings, such as conjunctiva, cornea, sclera, etc. Illustrations are relatively few and almost entirely consist of black-and-white drawings and diagrams. Although this makes the book less expensive, some doubt has been expressed whether texts such as this should be without colour. The patient's history could do with more emphasis, and it would have been appropriate to make this the opening section before 'Basic methods of examination.' Mention of the epidemiology of strabismus and glaucoma would have been appropriate to put these common conditions into context.

This very satisfactory new edition will be welcomed by ophthalmology postgraduates studying for higher examinations, especially the diploma in ophthalmology. It deserves its place in postgraduate ophthalmology as a concise text at a reasonable cost JAMES L KENNERLEY BANKES

Documenta Ophthalmologica Proceedings Series 38. Ophthalmic Ultrasonography. Proceedings of the 9th SIDUO Congress. Eds. J S HILLMAN and M M LE MAY. Pp. 502. £59·75. Junk: The Hague. 1983.

This volume is divided into three parts, 'The eye', 'The orbit', and 'Physics and techniques.' The first part opens with a section devoted to intraocular tumours. The role of ultrasound in the detection, diagnosis, and measurement of tumours, in particular of malignant melanomas, is discussed by several authors. Its value in determining extrascleral extension of tumours is also covered. The use of ultrasound biometry data to select the optimum orientation of eyes with malignant melanomas for proton beam irradiation was discussed by Lou and Gragoudas. Problems associated with the differentiation of choroidal haemangioma, metastases, and retinoblastoma are also covered. A section dedicated to vitreoretinal disorders contains some interesting material concerned with, for example, disciform (Byrne) and movement of the vitreous gel and retina (Susal and Walker)

Sections devoted to A-scan measurement of the eye contain a selection of both interesting and disappointing papers. Of particular note were papers concerning ultrasound velocity in different types of cataract (Loffredo *et al*), measurements in glaucomatous eyes (Bluth); a comparison of an ultrasonic and optical measuring system (Fledelius *et al*), and volume changes after encircling procedures (Zingirian *et al.*).

Part 2 of the book concerns the orbit and contains some well written papers but very little new material. Papers dedicated to blood vessels in tumours (Susal), the diagnosis of haemangioendothelioma (Byrne), and optic nerve tumours (Buschmann *et al.*) are worthy of mention. The final part of the book, on physics and techniques, is opened by Restori *et al* with a paper on interaction of sound pulses with tissue Haigis and Buschmann presented some worthwhile material about performance measurements on various ultrasound systems. An interesting paper on the use of a microcomputer based imaging system for volume measurement (Yamamoto *et al.*) is also to be found in this section.

These congress proceedings will be a valuable reference book for those working or planning to work in the field of ophthalmic ultrasound. It points out in a refreshing manner some of the pitfalls associated with ultrasonic diagnosis in ophthalmology. MARIE RESTORI AND DAVID McLEOD

Documenta Ophthalmologica Proceedings Series 40. 21st ISCEV Symposium, Budapest 1983. Pattern Electroretinogram, Circulatory Disturbances of the Visual System, and Pattern-Evoked Responses. Eds. JOHN R HECKENLIVELY, G H M VAN LITH, T LAWWILL. Pp. 328. No price given. Junk: The Hague. 1984.

The 21st symposium of the International Society for Clinical Electrophysiology of Vision (ISCEV) was held in Budapest in 1983 on the 25th anniversary of the foundation of the society (originally known as ISCERG). This volume is introduced by a history of the society written by Professor Harold Henkes, who was president in 1973–83.

In recent years it has been the custom to select specific topics for discussion, and these are indicated in the title. The pattern electroretinogram (PERG) was described many years ago, but with the introduction of electrodes that do not degrade the retinal image it is becoming a valuable clinical method. Lawwill reviews the technique in his invited lecture, and this is essential reading for anyone interested in the topic. There are several other good contributions on this subject.

The second topic, on circulatory disturbances, is less useful. There is still interest in the oscillatory potentials, which will surely become clinically more useful as their origins are elucidated. The final topic is the pattern evoked response. This could be contracted to the acronym PER, but as there are at least 25 others confusion over this procedure exists even before its complexities are considered. It is already a valuable clinical investigation, but for many reasons its experimental promise has not been realised.

Visual electrophysiology is a difficult and not generally known subject. This report will not be of general interest, but, with its predecessors, it is an invaluable guide to the literature. J H KELSEY

Glaucoma Surgery. By MAURICE H LUNTZ, RAYMOND HARRISON, HOWARD I SCHENKER. Pp. 149. £67·00. Williams and Wilkins: London. 1984.

In the early part of the 20th century the most successful glaucoma operation was that of iridectomy. Subsequent additions to the ophthalmologist's surgical repertoire have meant that in the late 20th century he has a bewildering array of operations to choose from when considering surgical control of this group of diseases. And no shortage of texts either. What the authors of this short text have done is to use their own considerable experience in glaucoma surgery to present us with 'an atlas approach' which they hope will act as a guide to the operations they use in the surgical management of the glaucomas. As the old adage concerning glaucoma surgery has it, 'the best glaucoma operation is the one which works in my hands.' This reviewer looked with interest to see what operations were recommended by these authors.

The book is not entirely an atlas. It gives a historical review of the surgery of congenital glaucomas, fistulising surgery, and combined procedures. It outlines concepts of pathogenesis of congenital glaucomas and glaucoma in aphakia. It gives indications for fistulising surgery (which include ocular hypertensives more than 65 years old with an IOP >26 mmHg, an enlargement of the C/D ratio to 0·6 or 0·7 (at whatever the IOP ?), and myopes with large saucer-shaped optic discs with IOPs >30 mmHg). In addition the section on congenital, infantile, and juvenile (CIJ) glaucomas is covered in greater depth than other glaucomas because of the 'paucity of available literature in these areas.'

The book is divided into two sections. Section 1 deals with the CIJ glaucomas and section 2 with adult glaucomas. In section 1 it is pointed out that these three types of glaucoma usually share a common developmental anomaly of the angle. The angle anomaly may be separated descriptively into mesodermal remnants (Barkan's membrane) and 'cicatrical' and iridocorneal dysgenesis. Although gonioscopic photographs well illustrate differences between the first two of these groups, this reviewer found the term 'cicatrical' difficult to understand in a primary glaucoma. The term suggests (postinflammatory) fibrosis, and, as the angle appearance suggests the formation of peripheral anterior synechiae, it might be clearer to call it trabeculodysgenesis. But this term has recently been suggested by Hoskins *et al.*[1] with a rather different meaning as to the final prognosis from that given by these authors.

In this section the authors state the importance of equating IOP readings obtained under anaesthesia with the clinical features. This is important, because they use halothane anaesthesia and schiøtz tonometry rather than ketamine and applanation tonometry as used elsewhere. They describe their operations for trabeculectomy well but dismiss goniotomy in only eight lines, for they do not use this operation.

Section 2 deals with adult-onset glaucomas. In this section the authors rely on their experience as justification for a described procedure usually without informing us of the insights or trials which led to its adoption. This is particularly important when they have to decide between using the trabeculectomy, Scheie's operation, subscleral Scheie, etc. The authors still find iridocycloretraction to be helpful despite reports to the contrary. They describe only intracapsular cataract extraction combined with trabeculectomy rather than extracapsular extraction and apparently do not insert intraocular lenses in these cases.

The book offers an atlas approach to glaucoma surgery. The reader must say to himself, 'These authors are experienced and this experience is their justification for performing the operations they recommend? Reader must provide their own answer to whether a particular operation is required for their own surgical repertoire. If it is, then they must ask, 'Can I perform operations X or Y after reading the description in this book?' For a number of the operations described the answer is a definite yes. The descriptions of trabeculotomy, trabeculectomy, iridectomy, subscleral Scheie, and combined intracapsular cataract extraction with trabeculectomy are good. Other operations are described sufficiently to give partial confidence to the would-be surgeon. For surgeons requiring these descriptions this book succeeds in its aim. ROGER A HITCHINGS

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Notes

European Ophthalmic Pathology Society

The 24th annual meeting was held in Basel, Switzerland, on 28–31 May 1985. Twenty-nine members and six guests were present including the guest of honour, Professor W C Frayer, representing the Verhoeff Society. The following cases were presented: W C Frayer (USA)· Tyrosinase-positive albinism A Tarkkanen (Finland): CHARGE association B Daicker (Switzerland)· Palpebral, orbital, and ocular anomalies in arhinencephalic syndrome E Landolt (Switzerland). Eye in Marfan's syndrome, and lens exfoliation syndrome (original case of Vogt). D de Wolff-Rouendaal (Netherlands, guest): A severe case of Rieger's syndrome. M Vogel (FRG): Wegener's granulomatosis. A Garner (UK)· Alveolar soft part sarcoma of the orbit E Balestrazzi (Italy)· Rhabdomyosarcoma of the orbit. G O H Naumann (FRG) Primary malignant melanoma of the orbit in congenital oculo-orbital-meningeal melanocytosis. O A Jensen (Denmark): Primary malignant melanoma of the orbit. W R Lee (UK). Merkel cell tumours of the eyelid A Nover (FRG): Papillary transitional cell carcinoma of the lacrimal drainage system. A Brini (France): Oncocytoma of the caruncle. H Offret (France)· Localised conjunctival amyloidosis. R Haddad (Austria). Fibre granuloma of the conjunctiva. M Quintana (Spain)· Bilateral lymphoid hyperplasia of the conjunctiva. G Goder (GDR): Mesenchymal tumour of the limbal conjunctiva. O Litrican (Yugoslavia): Keratoacanthoma of the conjunctiva. M Filipic (Australia, guest)· Abnormal collagen fibril structure in corneal deposits after treatment with indomethacin. R Barry (UK). Acanthamoebic keratitis. F Weber (Switzerland): Early changes in Reis-Bucklers' dystrophy. F Stefani (FRG): Pigmented cells on the anterior vitreous surface and zonules. R W Lyness (UK, guest): Senile degeneration of extraocular muscle. P Donders (Netherlands): Ring melanoma of the iris in a boy of 17. M Hanssens (Belgium): Failed photocoagulation of a choroidal malignant melanoma. A Hamburg (Netherlands): Sympathetic ophthalmitis and necrotic melanotic tumour in a pseudophakic eye. J Mullaney (Ireland): Pseudophacoanaphylactic endophthalmitis–? PMMA related J Prause (Denmark): Unexpected intraocular eosinophilia. O E Schnaudigel (FRG, guest). Retinal necrosis in AIDS. K Arnesen (Norway). Bilateral retinoblastoma in monozygotic twins E Kock (Sweden): Diffuse retinoblastoma in a 15-year-old boy diagnosed by vitrectomy. Z Latkovic (Yugoslavia): Diffuse infiltrating ocular tumour in a child. W Manschot (Netherlands)· An exceptional case of pseudoretinoblastoma. E Muneura (Spain, guest). Congenital toxoplasmosis. P Naeser (Sweden, guest)· Optic nerve involvement in a case of methanol poisoning. The meeting was organised by Professor B Daicker, and Professor A Tarkkanen presided.

Panhellenic congress

The 19th Panhellenic Congress of Ophthalmology will be held at Thessaloniki on 29–31 May 1986. The main topics are corneal surgery, laser surgery of the anterior segments of the eye, and contact lenses. Further information from: Ophthalmological Society of Northern Greece, POB 10497, 54110 Thessaloniki, Greece

Colour vision deficiencies

The 2nd Regional Symposium of the International Research Group on Colour Vision Deficiencies (IRGCV) will be held on 25–27 September 1986 in Deutsches Hygiene-Museum der DDR in Dresden, German Democratic Republic. Themes will include normal colour vision, examination methods, congenital defects, acquired defects, and practical aspects, and there will be free papers Details from Professor E Marré, Klinik fur Augenheilkunde der Medizinischen Akademie, GDR–8019 Dresden, Fetscherstraße 74, German Democratic Republic.

British Contact Lens Association

The new president of this association, Mr Keith Edwards, will give the presidential address at the Royal Society of Medicine on 19 September 1985. The title is 'The gas man cometh.'

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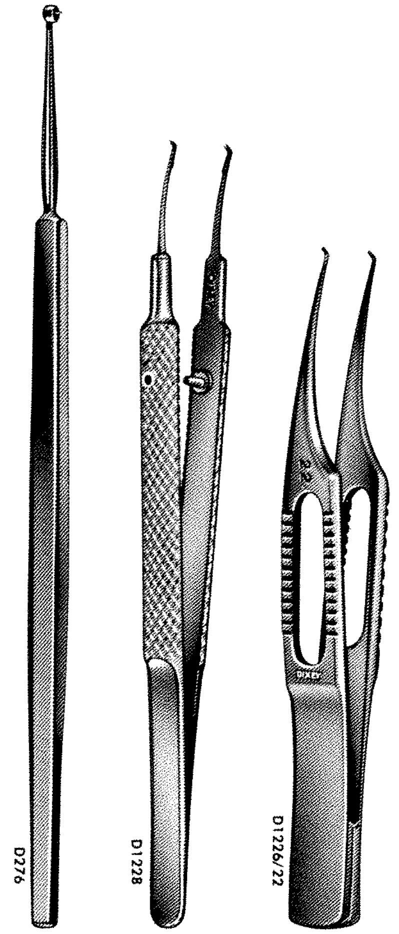

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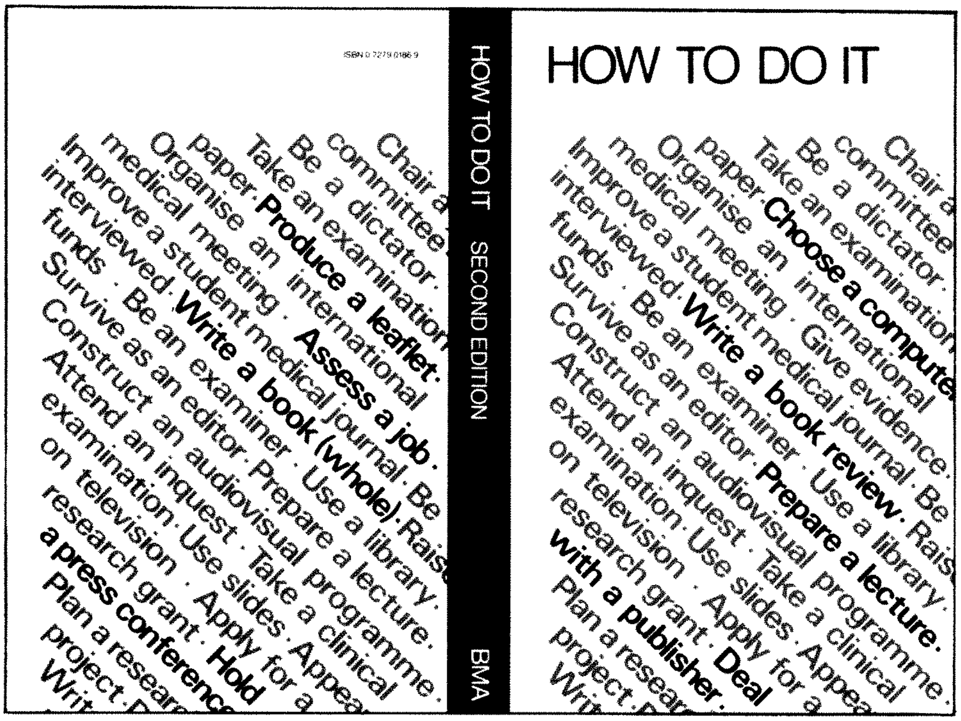

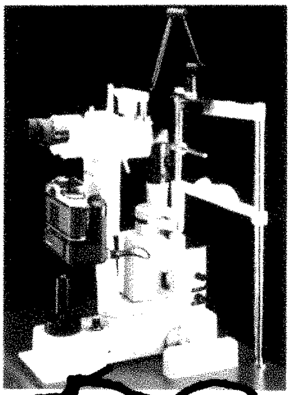

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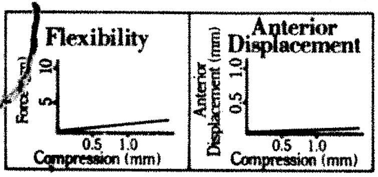

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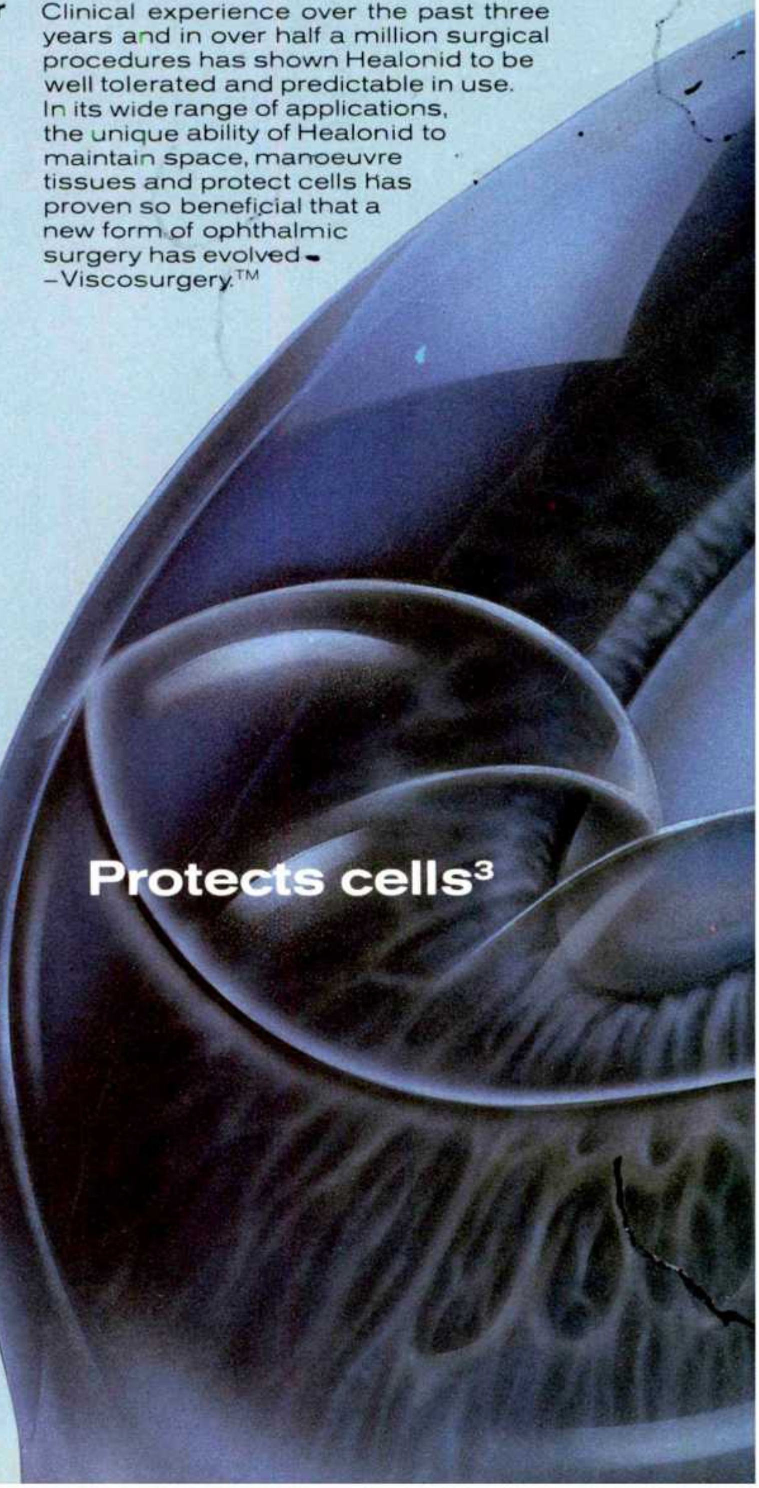

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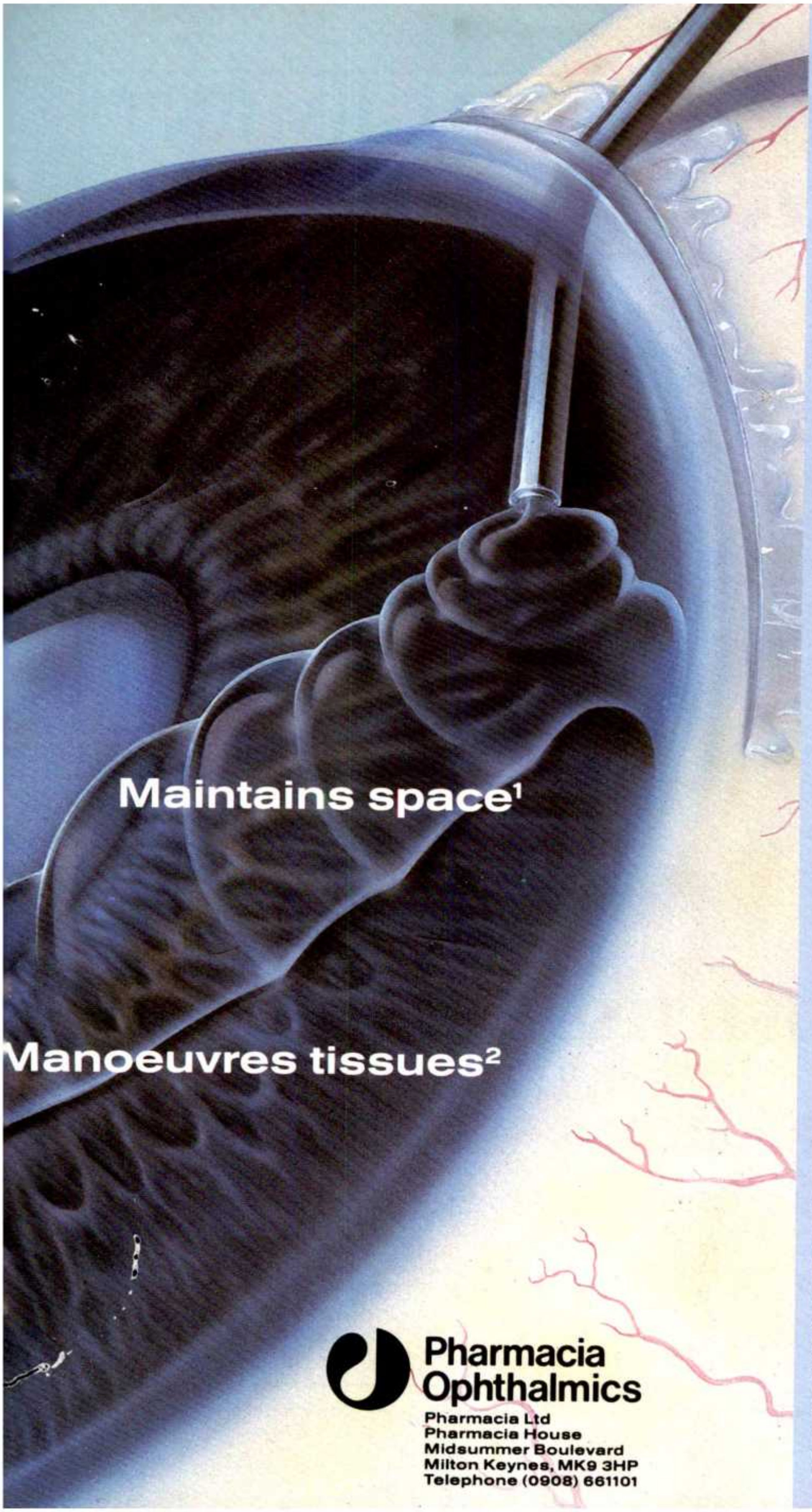

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LEGAL CATEGORY POM.

PACKAGING QUANTITIES AND BASIC N.H.S. PRICE (6th April 1984) Disposable syringes containing 0.4ml £29.44 each.

FURTHER INFORMATION
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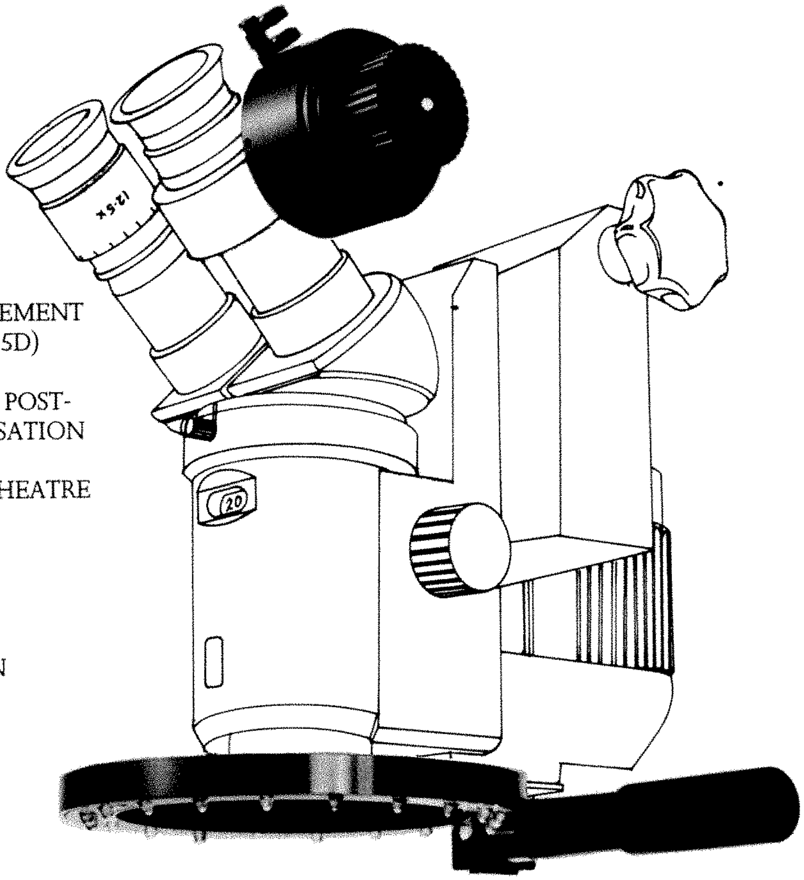

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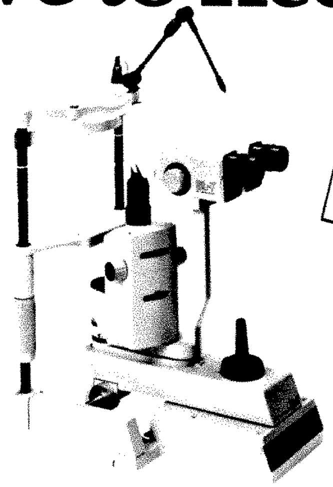

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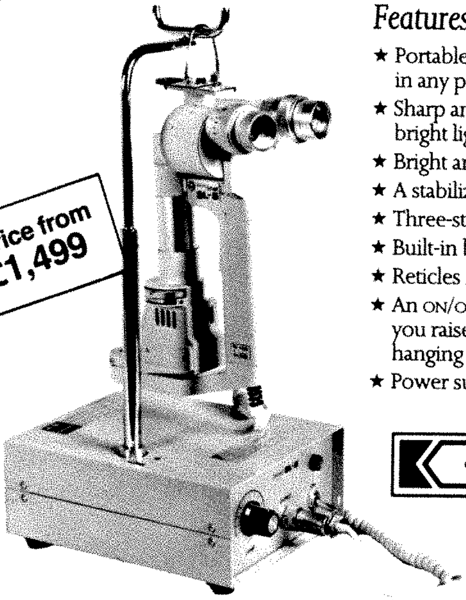

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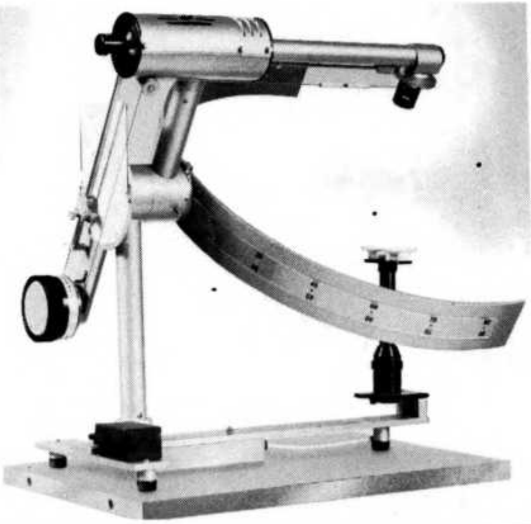

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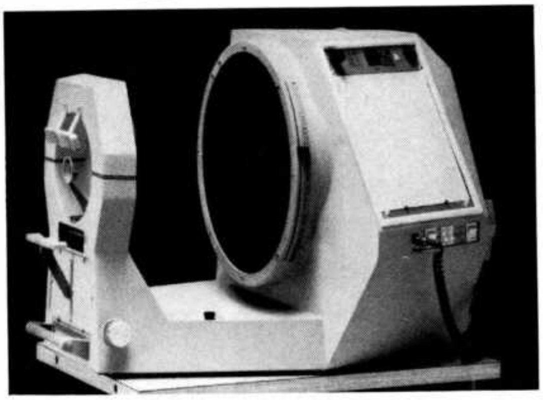

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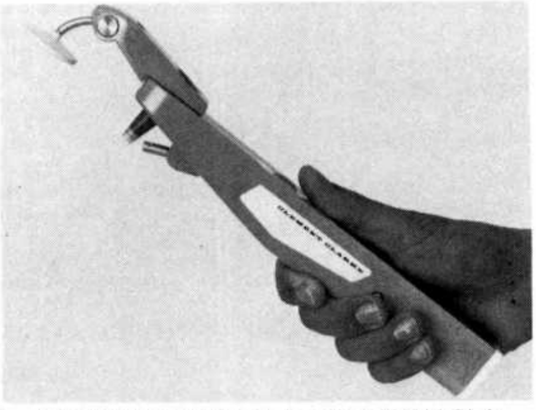

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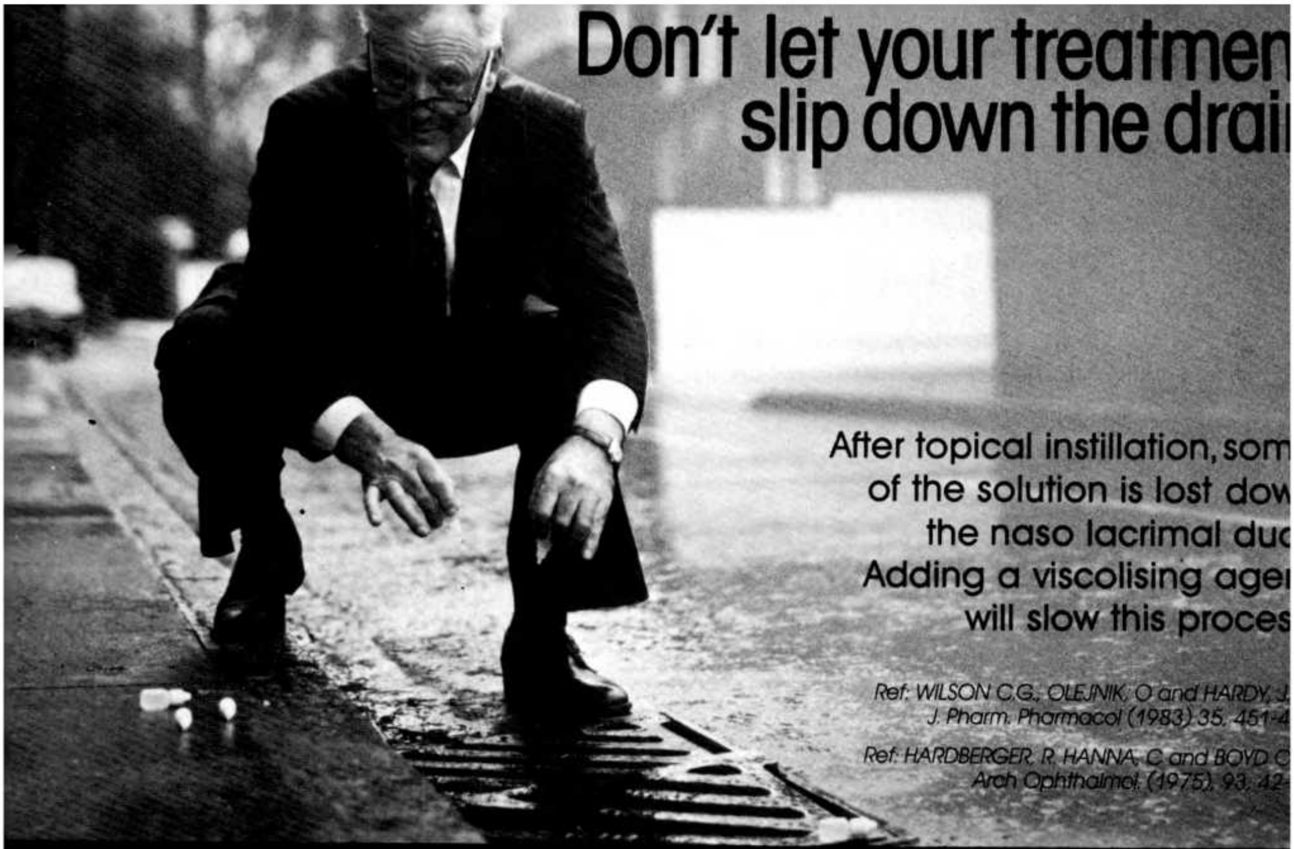

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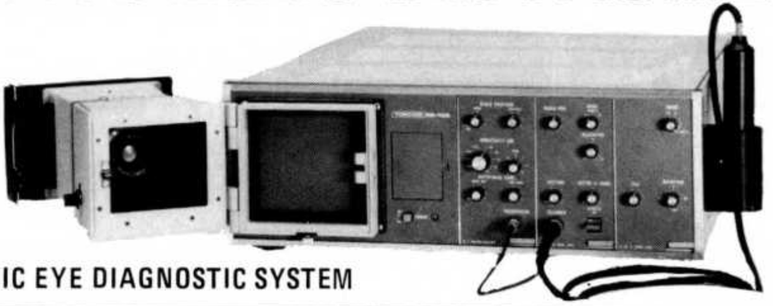

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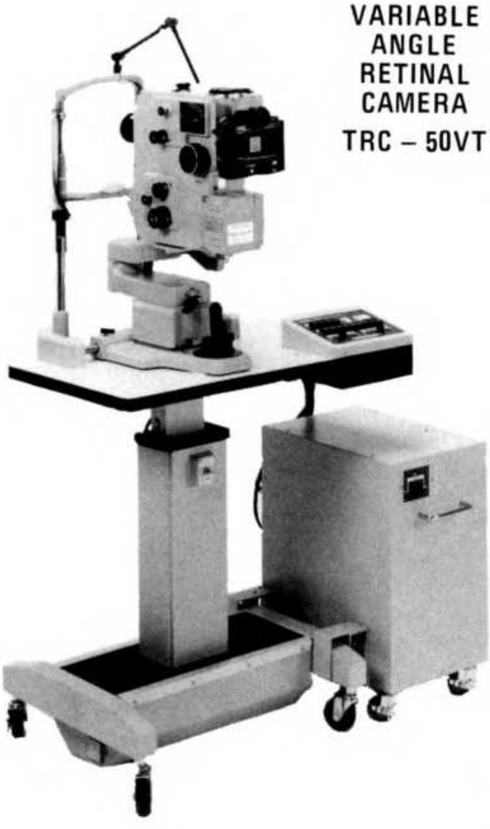

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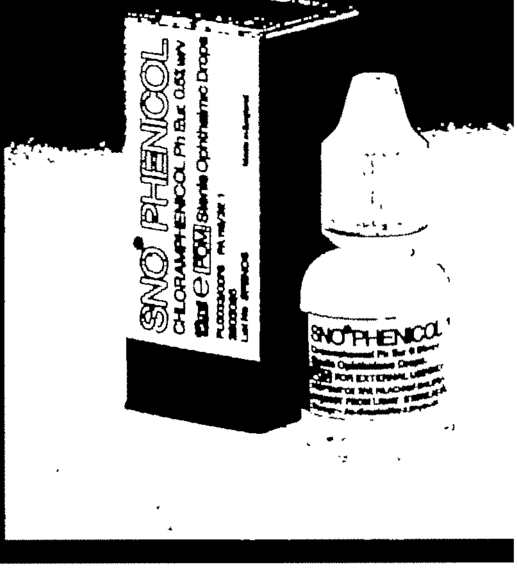

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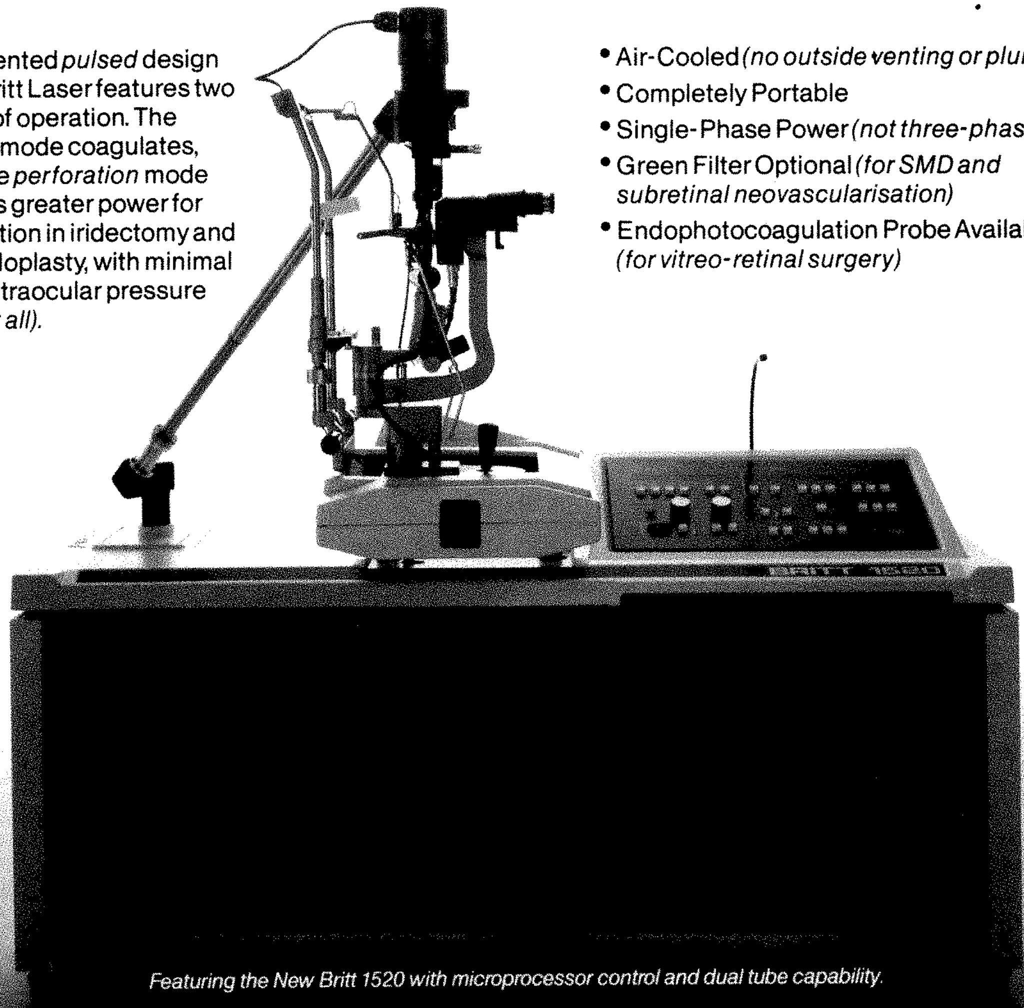

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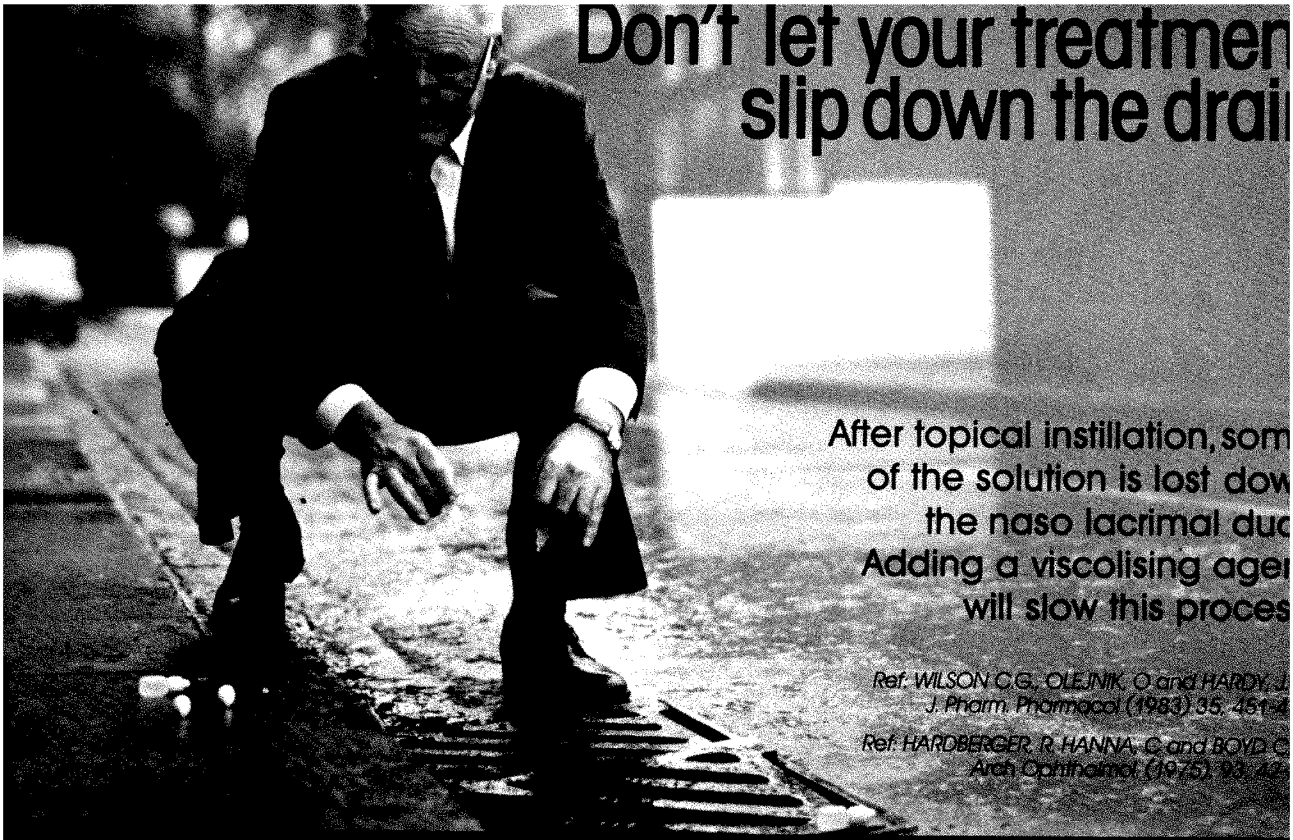

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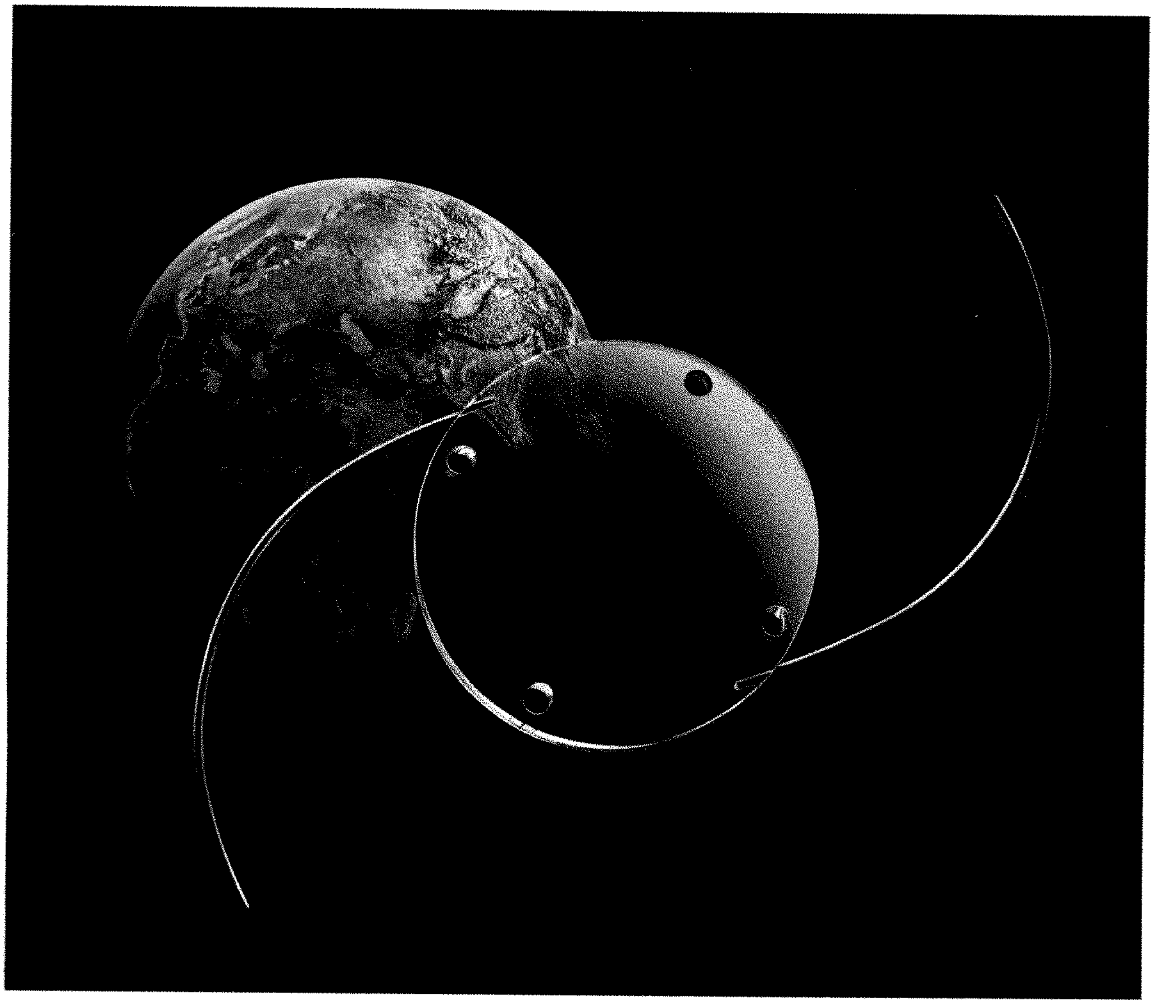

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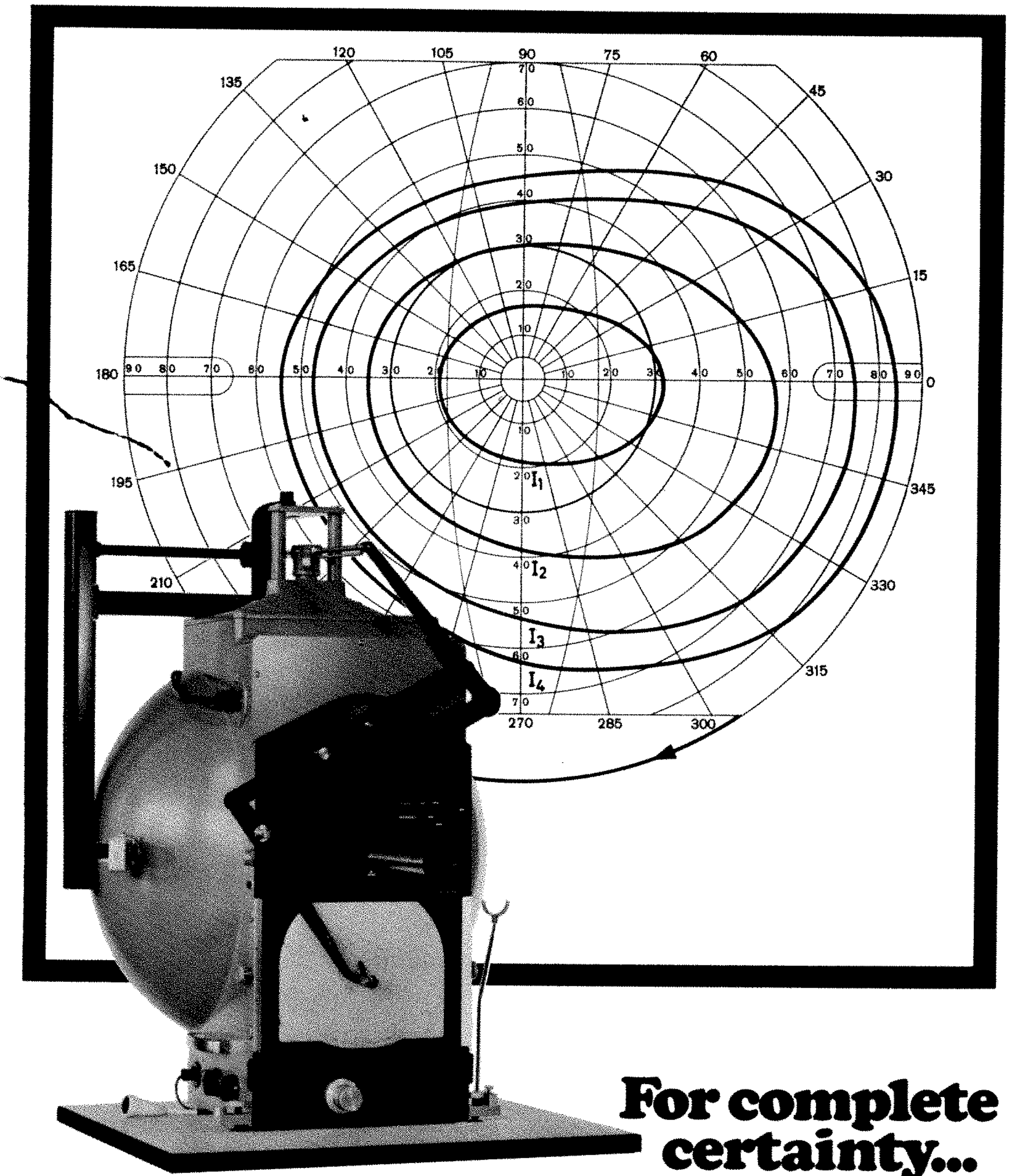

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British Journal of Ophthalmology, 1985, **69**, 717

Editorial: Sausages and squints

The pharmacological correction of strabismus has been a dream for many years. Recently it has become a reality for certain forms of squint because of the careful and persistent work by Alan B Scott at the Smith-Kettlewell Institute of Visual Sciences in San Francisco. In 1973 he published[1] the results of weakening the extraocular muscles in monkeys by injecting botulinum A toxin directly into these muscles. Botulinum toxin was chosen because over 90% of patients who had eaten spoiled sausage ('botulus' is Latin for sausage) or other food contaminated with *Clostridium botulinum* had diplopia as an early symptom in an often fatal, progressive, descending paralysis of bulbar and skeletal muscles. In 1980 Scott[2] published the first results of injecting botulinum A toxin into human extraocular muscle.

Over 1000 patients have now been treated in the USA and at selected centres around the world, including 85 adults in the report by Mr Elston and his colleagues in this issue of the *BJO*. So far no untowards systemic effects have been recorded. Three patients in the USA have had inadvertent perforation of the globe by the needle, but none lost the vision of that eye. Temporary levator paralysis may result from injection of the toxin into adjacent rectus muscles, with some slight local spread of effect. The aim of treatment is to control the degree of induced paralysis of the muscle by varying the dose used, and to control the duration of the paralysis by varying the dose and by repeated injections.

The results show that botulinum toxin therapy can be effective in young adults with moderate to large angles of squint. It is particularly useful in VIth nerve palsies when early injection of the medial rectus prevents contracture, and, if there should be no recovery of lateral rectus function, surgery is not needed on the medial rectus but only on those muscles that can restore abduction. A few patients without demonstrable fusion have developed or regained binocular vision after injection has produced incomitancy during the time of muscle paralysis, with the patient using his head posture to find a point where the two eyes can work together. Threatened anterior segment ischaemia if strabismus surgery were attempted can be avoided. Although, in general, the horizontal recti are more accessible to injection therapy than the vertical, patients with dysthyroid ocular disease respond well to treatment of the tight muscle(s) in the early stages of the condition. In the USA botulinum toxin is being used in children, even congenital esotropes less than 1 year old, with appropriate anaesthesia, and the results will be followed with great interest.

Apart from strabismus the toxin has been used in the treatment of patients with severely disabling neurogenic blepharospasm.[3] Here doses of approximately four times those needed in strabismus are given, with repeated injections into the orbicularis oculi being necessary, but the relief obtained without recourse to time-consuming surgery is high.

A new therapeutic agent has been found for the treatment of strabismus and blepharospasm. Further research into the neurophysiology of its action and clinical studies will establish its eventual role. It is fascinating that one of the most powerful toxins known can be used so effectively when properly controlled.

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PETER FELLS

British Journal of Ophthalmology, 1985, **69**, 718–724

Treatment of strabismus in adults with botulinum toxin A

J S ELSTON, J P LEE, C M POWELL, C HOGG, AND P CLARK

From the Institute of Ophthalmology and Moorfields Eye Hospital, London

SUMMARY Eighty-five adults with horizontal concomitant strabismus were treated with an injection of a low dose of botulinum toxin A (BTXA) into the lateral or medial rectus muscle. The ocular deviation was reduced by an average of 60% independently of its size and whether or not surgery had previously been performed. The change was temporary, however, except in those cases with binocular functions, when fusion was re-established. Repeated low dose injections can maintain the improvement, but at higher doses, although larger reductions are produced, temporary local side effects—ptosis and vertical strabismus—are common. The technique is simple, well tolerated, and has no systemic side effects.

Most adults considered for strabismus surgery have long-standing unsightly ocular deviations associated with amblyopia, no demonstrable binocular functions, and a history of one or more eye muscle operations in childhood.[1] The short term effect of further surgical treatment is unpredictable, and may reduce eye movements, while in the long term the strabismus frequently recurs.[2] The concept of chemically modifying extraocular muscle function in such circumstances is attractive, and botulinum toxin A has the necessary chemical and biological properties. Its manufacture and quantitation have been standardised, and animal experiments have established that an appropriate dose injected directly into a skeletal muscle causes local paralysis without systemic toxicity.[3,4] Individual extraocular muscles can be selectively weakened in the rhesus monkey, producing a strabismus, and although the treated muscles recover full function there is a permanent change in the ocular alignment.[5] The toxin is immunologically inert at the doses used and can be repeatedly injected.[6]

The clinical application of botulinum toxin A was established in 1980 by Scott,[7] who showed that an extraocular muscle in a patient with strabismus can be effectively weakened under local anaesthesia, allowing the deviated eye to move into alignment. Several hundred patients ranging in age from 5 months[8] to 80 years have since been treated in the United States under Scott's sponsorship, and no adverse systemic effects have been reported. The long term results, however, are not yet established. The results of the treatment of 85 unselected cases of adult strabismus with botulinum toxin A as an alternative to surgical treatment are reported. The follow-up period is from 12 to 20 months.

Patients, materials, and methods

Eighty-five patients aged 18 to 72 scheduled for surgery for horizontal concomitant strabismus accepted the alternative of treatment with botulinum toxin injections (Table 1). Informed consent was obtained, and the patients reserved the right to withdraw from the trial or ask for surgical treatment

Table 1 *Clinical features of patients treated*

Total	85
Male	31
Female	54
Age range	18–72 years
Average age	40 years
Esotropia	37 cases
Exotropia	48
Amblyopia	46
Previous surgery	66
Binocular functions demonstrable	2
Average pretreatment deviation	50 prism dioptres

Amblyopia was defined as a difference between the two eyes of two or more lines Snellen chart best corrected acuity without structural abnormality of the fundus or anterior visual pathway.

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at any stage. There were 37 cases of esotropia and 48 cases of exotropia, 20 of whom had had surgery for esotropia. Sixty-six patients had undergone strabismus surgery in the past, 28 having a history of two or more operations to a maximum of five to correct their deviation (Table 1). The angle of strabismus was measured by prism cover test at near and distance fixation, or by corneal reflections if fixation was poor. Binocular functions were investigated and the range of eye movements noted.

Botulinum toxin A in ampoules containing 0·05 μg freeze dried neurotoxin bound to haemagglutinin was reconstituted with 1·0 ml preservative-free sterile saline, and then diluted to give either $3{\cdot}12\times10^{-4}$ μg or $1{\cdot}56\times10^{-3}$ μg of neurotoxin in 0·1 ml of solution. Amethocaine 1% local anaesthetic, 4 drops, was instilled in the conjunctival sac, and adrenaline 0·25%, 1 drop, to constrict the conjunctival vasculature and allow the extraocular muscle to be easily seen. The toxin was injected through a 27 gauge needle with polytetrafluoroethylene insulation except at the tip, which constituted the active electrode of a differential pair, the reference and ground electrodes being standard silver:silver chloride electrodes taped to the brow, with the reference electrode over the eye to be treated. The needle tip was passed through the conjunctiva, then posteriorly alongside the muscle until the equator of the globe was passed, when it was angled into the muscle.[7] An electromyographic (EMG) signal was recorded from the needle tip and allowed the appropriate muscle to be identified when activated by the patient's voluntary gaze.

All patients were treated with a dose of $3{\cdot}12\times10^{-4}$ μg neurotoxin into the muscle (lateral or medial rectus) responsible for the deviation of the eye; orthoptic measurements were repeated at one, two, four, and eight weeks. If the initial response was inadequate, after its paretic effect had worn off, $1{\cdot}56\times10^{-3}$ μg neurotoxin was injected into the same muscle and the follow-up schedule repeated. When the appropriate dose of neurotoxin for the individual patient had been established, injections were repeated if the strabismus recurred to a cosmetically unsightly extent.

STATISTICAL ANALYSIS

Stepwise regression was used to determine whether any other variables could help to explain the initial angle of the strabismus or any changes in the angle. The initial angle and both the actual and proportional changes at one, two, four, and eight weeks were chosen as dependent variables. The age and sex of the patients, the direction of the strabismus (esotropia or exotropia), and previous surgery were used as explanatory variables. The initial size was also used as an explanatory variable when the changes in strabismus were used as dependent variables. A partial F ratio of 4 was used to determine inclusion and exclusion of variables in the model.

Results

From March to December 1983, 85 patients were enrolled in the study. The ocular deviations were large, with a high incidence of amblyopia and attempted surgical correction, and binocular functions were demonstrable in only two (Table 1). The size of the initial strabismus was related to the age of patients, with older patient having larger deviations (Fig. 1). Stepwise regression showed that no other explanatory variable had any effect.

The ocular deviation was regarded as abolished if over the period of follow-up the cover test was

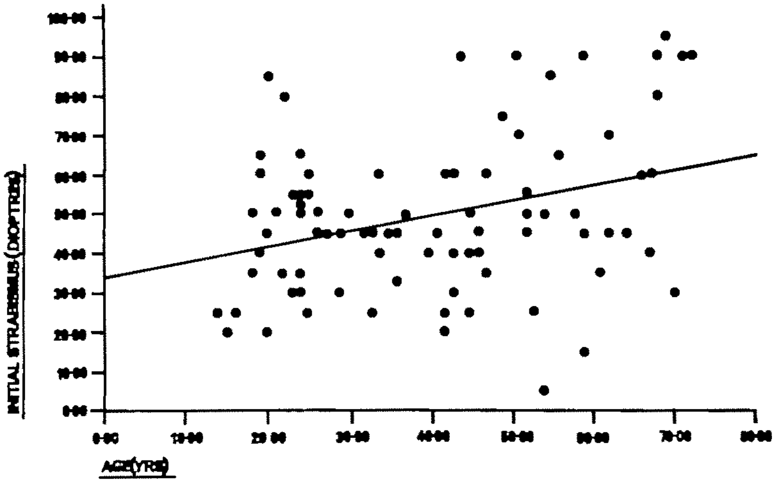

Fig. 1 *Size of strabismus before treatment related to age of patient*

Table 2 *Mean reduction in strabismus over time in weeks*

	Weeks			
	1	*2*	*4*	*8*
Number of patients	85	84	68	43
Actual (prism dioptres)	23·46	34 04	29·00	24·67
SE	1·87	2·47	2·76	2 83
Proportional	0·43	0 62	0·61	0·46
SE	0·054	0·044	0 046	0·163

SE=standard error of the mean

negative and full binocular function demonstrable, and as acceptable if it was stable, measured no more than 50% of the pretreatment angle, and the patient was satisfied with the appearance. The deviation was designated recurrent if any measurement was greater than 50% of the pretreatment angle.

The maximum change in the angle of the strabismus after one injection occurred at two and four weeks, and averaged 34 prism dioptres (Table 2) but was larger in patients with larger pretreatment angles (Fig. 2). No change in the angle was recorded in two cases after treatment, the injection had not been made into the muscle, however, since no weakness was produced. The proportional change was relatively constant and averaged 60% of the original deviation (Fig. 3). The sex of the patients, the direction of the deviation, and previous surgery had no influence on the findings. At this stage the eye movements and saccadic velocity in the direction of action of the injected muscle were reduced. The proportional reduction in strabismus lessened over the next six weeks (Fig. 3), by which time full eye movements were restored and a further injection could be considered.

There were no systemic complications. In four cases local spread of paralytic effect within the orbit was observed—an incomplete paralysis of the upper lid levator giving a partial ptosis in three cases, and an inferior rectus weakness in one—with complete recovery within six weeks. In 2 cases, with full binocular potential, the deviation was abolished by one injection.

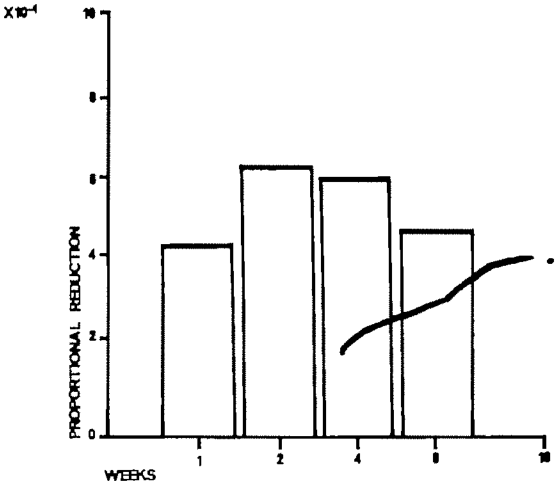

Fig. 3 *Proportional reduction in strabismus declines from two weeks after the first injection*

CASE I

A 19-year-old girl suffered an attack of idiopathic inflammatory polyneuropathy (Guillain-Barré syndrome) in January 1983 associated with a right lateral rectus palsy. She recovered completely, but had a residual right esotropia of 60 prism dioptres associated with intermittent right suppression (Fig. 4A). The right medial rectus was treated with a single dose of $3{\cdot}12\times10^{-4}$ μg BTXA, producing a consecutive exotropia of 40 prism dioptres after two weeks, when

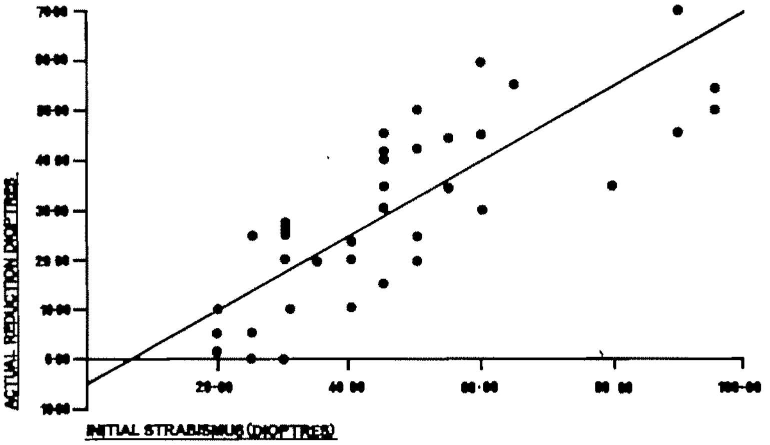

Fig. 2 *Actual reduction in strabismus four weeks after first injection.*

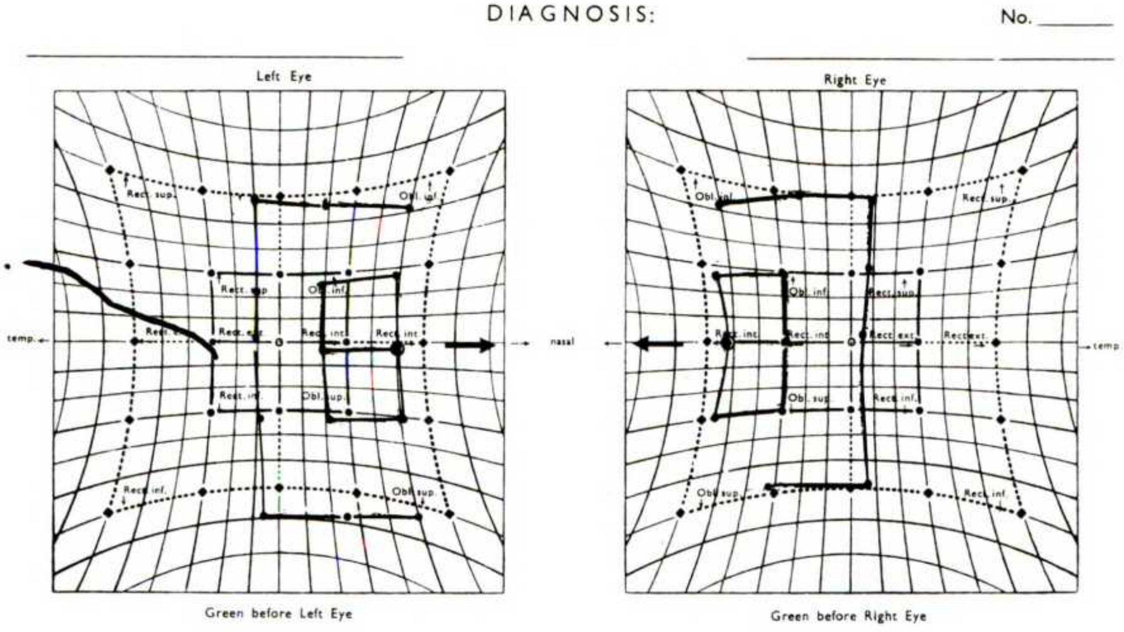

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Fig. 4A

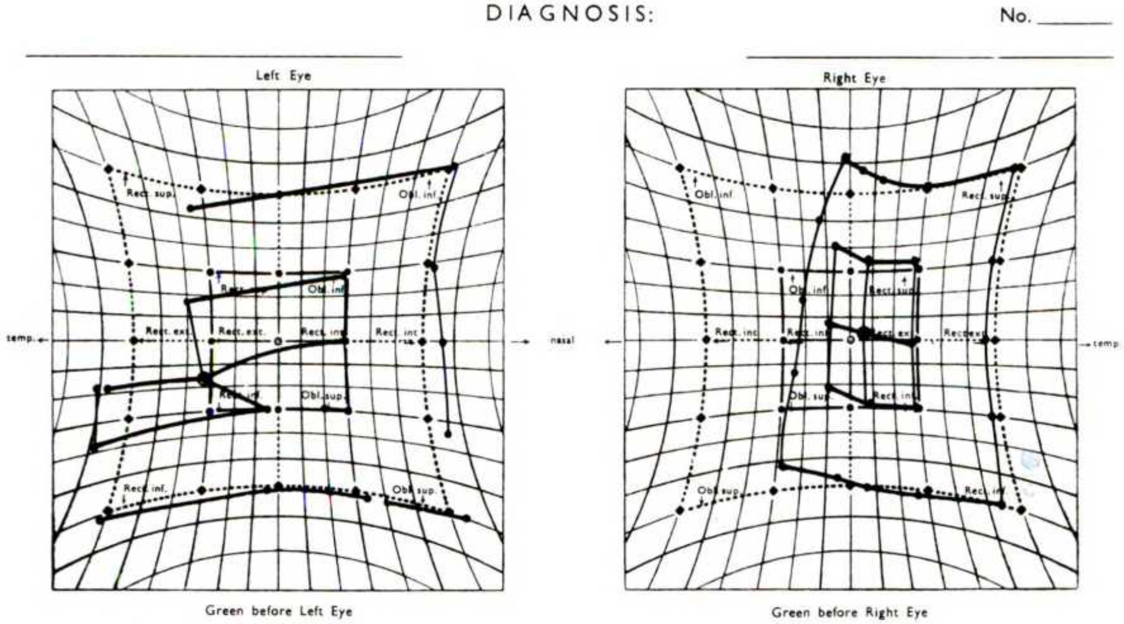

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Fig. 4B

Fig. 4 *Case 1. Serial Hess charts showing the re-establishment of normal binocular function.* A: *Pretreatment.* B: *Two weeks after treatment.* C: *Twelve weeks after treatment.*

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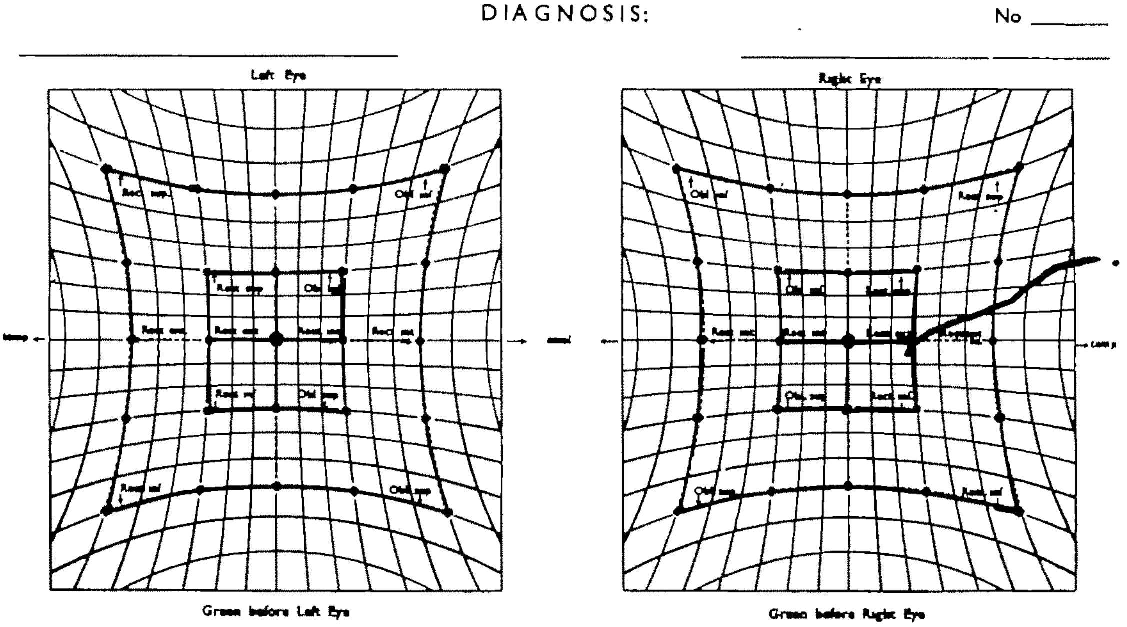

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Fig. 4C

binocular functions were re-established with the head turned to the left (Fig. 4B). Six weeks after the injection nearly full right adduction had returned, and at 12 weeks no abnormality of the oculomotor system was detectable (Fig. 4C).

Table 3 *Treatment of recurrent deviations: high and low dose schedules*

	High dose *1·56×10⁻³ μg* *BTXA*	*Low dose* *3·12×10⁻⁴ μg* *BTXA*
Total number	21	44
Average age (years)	48·5	37·5
Average pretreatment deviation (prism dioptres)	70	43
Esotropia	6	24
Exotropia	15	20
Average maximum change in deviation after second injection (prism dioptres)	38·5	22·5
Side effects partial ptosis or vertical deviation	10	6
Deviation abolished	2	0
Deviation acceptable with continued treatment	9	36
Average total injections required per year for maintenance	2·5	3·2
Withdrew from trial·		
no further treatment	10	4
surgical treatment	3	4

In eight cases the deviation was reduced to an extent acceptable to the patient. Follow-up measurements have shown a gradual return to the pretreatment strabismus over three months. Eight of the remaining 75 patients declined any further treatment, while two accepted surgery and 65 further injections. Twenty-one patients were treated on the high dose schedule; they were older and had larger squints than those on the low dose schedule. The maximum change in the angle of strabismus achieved on the second injection into the previously treated muscle averaged 38·5 prism dioptres. There was a high incidence of temporary partial ptosis and vertical muscle underaction due to orbital spread of BTXA from the treated muscle (Table 3). Over half the patients declined further injections and withdrew from the trial or opted for surgical treatment. The strabismus was unexpectedly abolished, however, in two cases, in which binocular functions had not been demonstrated before treatment. Nine patients have maintained an acceptable reduction in the deviation, requiring an average of 2·5 injections over the first year of follow-up to do so.

On the low dose schedule there were fewer side effects, and only one-fifth of the patients either withdrew from the trial or asked for surgery. The second injection resulted in an average change of 22·5 prism dioptres. However, a larger number of injections has been required to achieve an acceptable reduction in strabismus.

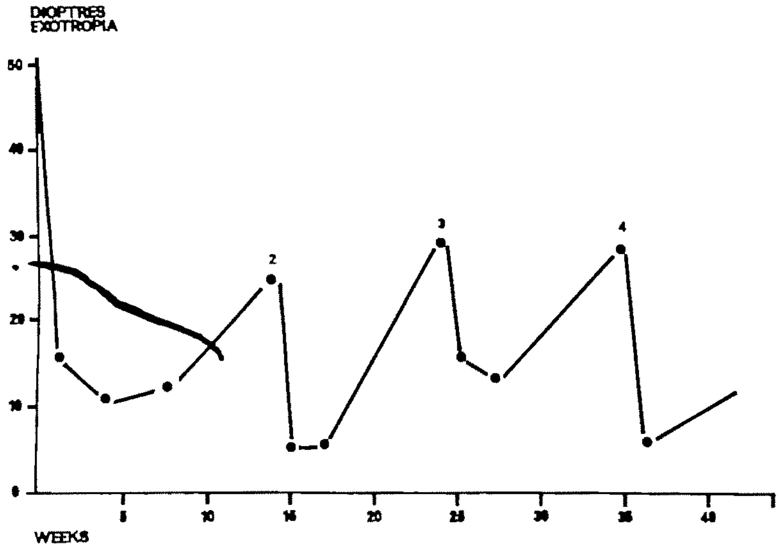

Fig. 5 *Case 2. Treatment of recurrent consecutive exotropia by repeated injection (numbered) of BTXA into the right lateral rectus*

CASE 2
An 18-year-old female student had treatment for a right convergent squint and amblyopia with glasses, patching, and three operations in childhood. At the age of 15 an operation for consecutive exotropia was carried out on the right eye, but the strabismus recurred and measured 50 prism dioptres. A total of four injections have been given into the right lateral rectus without side effects (Fig. 5).

Discussion

Motor nerve terminals contain acceptors which specifically bind botulinum toxin A and mediate its internalisation, where it prevents acetylcholine release, probably by lysosomal processing.[10] The neuromuscular blockade is permanent,[11] and muscle function recovers by the sprouting of new motor end plates from the axon,[12] a process that takes longer in fast (twitch) skeletal muscles, which predominate in the extraocular muscles, than in slow (tonic) fibres.[13] The intensity and duration of the flaccid paralysis of the extraocular muscle is therefore dependent on the dose of toxin injected. These results show that a single low dose of botulinum toxin A predictably alters the position of the eye within the orbit by selectively weakening the rectus muscle, independent of the size, direction, and previous treatment of the strabismus. If motor fusion is re-established, the deviation will be abolished. In general, however, the alteration is not sustained, and repeated injections are necessary. On the high dose schedule, in cases of large, longstanding strabismus, fibrosis and contracture of the muscle combined with reduced ocular movements and often exacerbated by previous surgery contribute to the poorly sustained response. The high incidence of side effects further limits the application of the technique in such cases. Repeated injections on the low dose schedule achieve a satisfactory stable improvement in younger patients with comparatively small deviations.

Two factors probably contribute to the sustained response: during the period of induced paralysis the ipsilateral antagonist rectus muscle develops contracture changes analogous to those sometimes seen in the medial rectus in cases of temporary lateral rectus palsy.[14] At the same time, even after full recovery from the paralysis, there is a permanent disturbance of the pattern of motor innervation in the treated muscle.[15] After repeated injections, the neuromuscular balance between the two opposing horizontal rectus muscles may be altered in favour of the untreated muscle and the strabismus reduced.

Surgical treatment of the patients in this study (average deviation 50 prism dioptres) would involve operating on two or three horizontal rectus muscles under general anaesthetic. Botulinum toxin treatment is shown here to be a safe and simple alternative, effective in younger patients with moderate to large strabismus. Longer follow-up will further define its therapeutic role.

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Objective evaluation of sensorial and sensorimotorial status in esotropia: their importance in surgical prognosis

B BAGOLINI

From the Ophthalmic Clinic of the Catholic University, Rome, Italy

SUMMARY Appropriate use of base-out prisms may be a useful objective test for detecting persistence of normal binocular vision (4-dioptre prism test). By prolonged observation of prismatic correction of an esotropic patient one may infer the presence of an anomalous sensorial status. This can be done when the prismatic correction is compensated for by an increase of the angle of esotropia (prism adaptation test). The increase in the angle of esotropia induced by base-out prisms, here called anomalous movements, is probably related to a type of anomalous movement fusional in nature. When anomalous movements are present, it is important to realise how powerfully they have developed. This may be inferred by determining what amount of prism overcorrection of the esotropic angle the patient is capable of compensating for (progressive prism compensation test). This has important implications for surgery. It has been statistically demonstrated that esotropia with strong anomalous movements tends to respond less effectively to surgery than esotropia without or with weak anomalous movements.

In strabismus we generally want to know if normal binocular single vision can be restored and how much surgery should be performed Some functional subjective tests can be usefully attempted when the patient is sufficiently co-operative. There are, however, a series of objective tests which are useful for inferring both the binocular status and the possible reaction of the patient to corrective surgery. These objective tests can be applied in quite young children when their span of attention lasts at least a few seconds.

The binocular adaptational phenomena occurring in strabismus are purely sensorial, such as suppression, anomalous retinal correspondence (ARC), and sensorimotorial, such as anomalous movements (AM).

Sensorial adaptational phenomena

Suppression prevails in large-angle deviation, while anomalous correspondence with achievement of an anomalous binocular vision prevails in relatively small-angle deviation. This anomalous binocular vision is detectable mainly under conditions as close as possible to casual seeing (such as can be observed by the striated glasses test) and is frequently interrupted by more dissociating tests.[1-7]

Sensorimotorial adaptational phenomena

Haldén[8] demonstrated fusional movements in anomalous correspondence. This author in a very interesting piece of work has demonstrated fusional movements in strabismus in spite of an abnormal binocularity. Though his experimental conditions in the light of subsequent knowledge were open to criticism,[9] his final conclusions must be considered valid.

I have studied clinically the same movements,[10] observing the behaviour of the angle of deviation in esotropic patients whose angle had been corrected by base-out prisms. It has been seen that the prisms are slowly compensated for in many cases of esotropia. The angle sometimes increased, compensating the full correction of the esotropic angle, and in many cases strong prismatic overcorrection could also be compensated for with a remarkable increase of the angle of deviation; the angle returns to its original preprismatic value after a variable period of several

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minutes from patient to patient. This phenomenon is considered a sensorimotorial sequela of strabismus because with appropriate exercises it can be minimised or eliminated.[11-13] It is also considered to be an expression of anomalous fusional movements in the sense that the retinal elements of the deviated eye tend to change not only their directional localisation in binocular vision (ARC) but also their motorial value[10] (Bagolini and Zanasi, in preparation).

The aim of these ocular movements appears to be that of bringing the two retinal images, of the object that the patient is looking at, over retinal areas in the two eyes which have become anomalously correspondent (having therefore acquired the same directional localisation). However, directional localisation and motorial value in patients with strabismus do not necessarily change at the same time, as can be demonstrated in some cases which show ARC but do not compensate for prisms or more rarely vice-versa. The fact that base-out prisms tend to determine convergent movements while base-in prisms elicit divergent movements and vertical prisms vertical movements[14] seems to prove the fusional nature of these disjunctive movements. In order not to commit myself, however, on their interpretation I shall call them 'anomalous movements' (AM). They are slow in comparison with normal fusional movements, and they cannot be seen with the naked eye. They can be detected only after base-out prisms have been worn for minutes or hours. Their detection becomes possible only by the cover test, when prismatic correction or overcorrection has been partially or totally compensated for by an increase in the strabismic deviation.

EFFECT OF ANOMALOUS MOVEMENTS ON SURGERY

AM are elicited in esotropia by base-out prisms. The adequate stimulation is a displacement of the retinal images. The same retinal displacement occurs after corrective surgery. We can therefore expect an increase in the medial recti tonus either by using base-out prisms or by carrying out corrective surgery. If the AM are very powerful and thus make the patient compensate for very strong prisms, we should expect less surgical corrective effect. It has to be pointed out that in cases with strong AM patients are operated on for cosmetic reasons only. We know in fact from clinical experience that, when AM are present and powerful, they are an expression of an irreversible anomalous sensorial and sensorimotorial situation.

A "progressive prism compensation test" (PPT) has been developed in order to study the strength of the AM. The angle of esotropia is first corrected by base-out prisms. The patient is observed for a period ranging from a few minutes to two hours. If the angle deviation has not increased, no AM have developed. If the angle of strabismus has increased and the prisms have been compensated, it means that AM are already present. We further increase the amount of prismatic correction by steps from 5 to 10 prism dioptres, observing the patient till no more compensating movements take place.

It is possible to find patients that compensate for even a prismatic overcorrection of their original esotropia up to 50 and 60 prism dioptres. AM are strongly developed in these cases.

Material and methods

Sixty one patients with esotropia from 5 to 8 years of age were tested with the PPT. All of them had full hyperopic correction and had approximately equal vision in the two eyes; the angle for distance ranged from 12 to 22 prism dioptres of esotropia.

Cases with an angle variable more than ±3 dioptres were discarded. No patient had normal fusional movements and all showed ARC with the striated glasses and at the synoptophore. The surgical procedure for all cases was a recession ranging from 4 to 5 mm of one medial rectus.

Results

The graph shows the results (Fig. 1). In the vertical axis the percentage postoperative decrease in the angle deviation is indicated and in the horizontal axis there is the maximum amount of prism the patients were capable of compensating for before surgery. When the angle of strabismus decreased by over 100% they were overcorrected. It is evident from the graph ($p<0{\cdot}001$) that in patients who compensated for a large amount of prism the corrective surgery was less effective than in patients who compensated for a small amount of prismatic correction.

Discussion and conclusion

It appears that binocular adaptational phenomena in strabismus are not only sensorial (suppression and ARC) but also sensorimotorial (AM). Suppression and ARC can be studied only with subjective methods. AM can be objectively studied with prisms, and when they are present they can be considered an objective proof of an anomalous situation; subjective tests are therefore not necessary when AM are clearly present. Prisms are then an important tool for detecting objectively the state of binocular vision and for predicting the effect of surgery in cases where there is no further possibility of restoring normal binocular vision.

Summarising the use of prisms for the objective

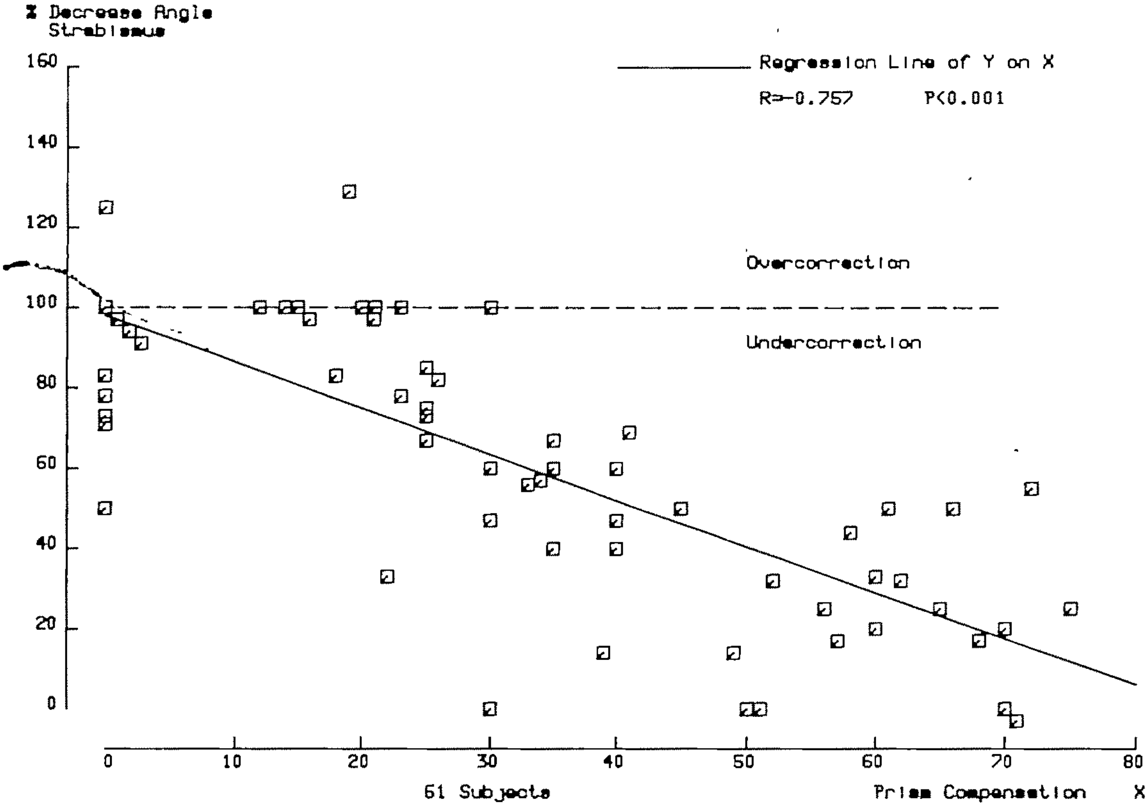

Fig. 1 *The preoperative prism compensation from 0 to 80 dioptres going from left to right is indicated in the horizontal axis The postoperative percentage of improvement, indicated for the various patients by the symbol □, is plotted against the preoperative amount of prism compensation. Above the line of 100% correction, indicating orthotropia, are located the overcorrected cases. The greater the prism compensation the less was the surgical correction obtained (p<0·001)*

study of the sensorial and sensorimotorial status of an esotropic patient, we recommend, the following three tests.

(*a*) Four-dioptre prism test of Irvine,[15] popularised by Jampolsky[16] (for description of this test see von Noorden and Maumenee's *Atlas*[17] and for criticism von Noorden and Romano[18]). When normal fusional movements do not take place at the 4-dioptre prism test, this is taken as evidence of suppression by the above mentioned authors. However, if the test is performed while using the striated glasses, two conditions are found. First, the patient may actually suppress and will see only one strip or only part of the other. In this case the Irvine test is an expression of suppression. Secondly, the patient may see two strips crossing the light. There is no suppression in this case. When the 4-dioptre prism is placed in front of one eye, there are no fusional movements, but the patient may continue to see a light crossed by two beams. We are not inside a suppression area but inside an area of anomalous binocular vision (as demonstrated by Bagolini[4 9]) in which one point of the fixing eye may potentially correspond to a large retinal area in the deviated eye. A similar thing may occur in A or V pattern when the patient, with the striated glasses, may continue to see one light crossed by two beams both in up and down gaze.[19 20]

When a 4-dioptre prism is placed in front of one eye and the reaction is a fusional movement, we know there is normal binocular vision. The test is in this case positive. If no fusional movement is present, the patient has no normal binocular vision. This test can be performed in patients with straight eyes in whom we do not know if they are orthophoric or orthotropic. It can also be done on esotropic patients in whom the eyes have been straightened with glasses or if the deviation is not too large and not purely accommodative, in eyes which have been straightened with corrective prisms on a trial frame.

The 4-dioptre prism test can be performed over the glasses in the first case and over the prismatic correction in the second case. In this second case, however, only seldom and only if the squint is of recent origin will the test indicate maintenance of normal binocular vision.

(*b*) The second prismatic test that should be mentioned is the prism adaptation test of Jampolsky[21] (PAT). This should be performed in esotropic patients, in whom the Irvine test is negative, and has been devised as an objective method for determining whether the sensorial status is anomalous In this test the angle of esotropia is corrected with prisms and is observed from several minutes to one or two hours. When there is compensation of the prism correction, this is a proof of an anomalous sensorial status.

(*c*) The third prismatic test is the progressive prism compensation test (PPT) described above. When the PAT is positive the strength of the AM is studied by progressively overcorrecting with base-out prisms the angle of esotropia up to an amount where the patient is no longer capable of compensating by overconverging. In this last case normal binocular vision is obviously not present and increasingly less restorable. Moreover, the test gives an indication of how the patient may react to surgery.

Powerful AM appear to be one of the various factors rendering surgery in strabismus unpredictable and add uncertainty to any formula based on geometrical reasoning or on clinical experience. To improve predictability in surgery performed on esotropic patients with powerful AM it is advisable to try to eliminate this strabismus sequela with appropriate exercises[11-13] (Bagolini and Zanasi, in preparation).

I thank Mrs M R Zanasi, who made the preoperative and postoperative measurements, and Ing R Bolzani, who did the statistical evaluation.

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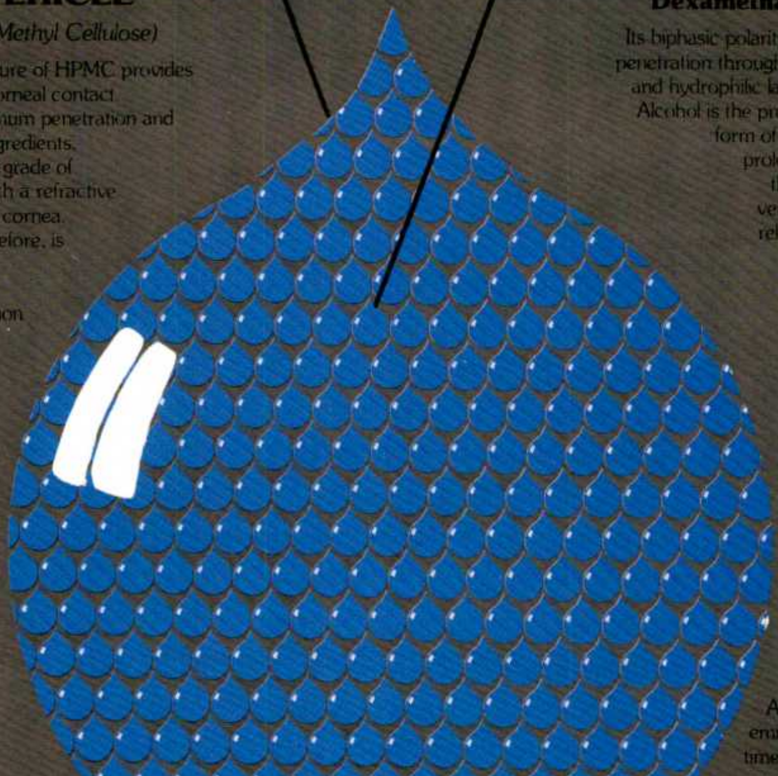

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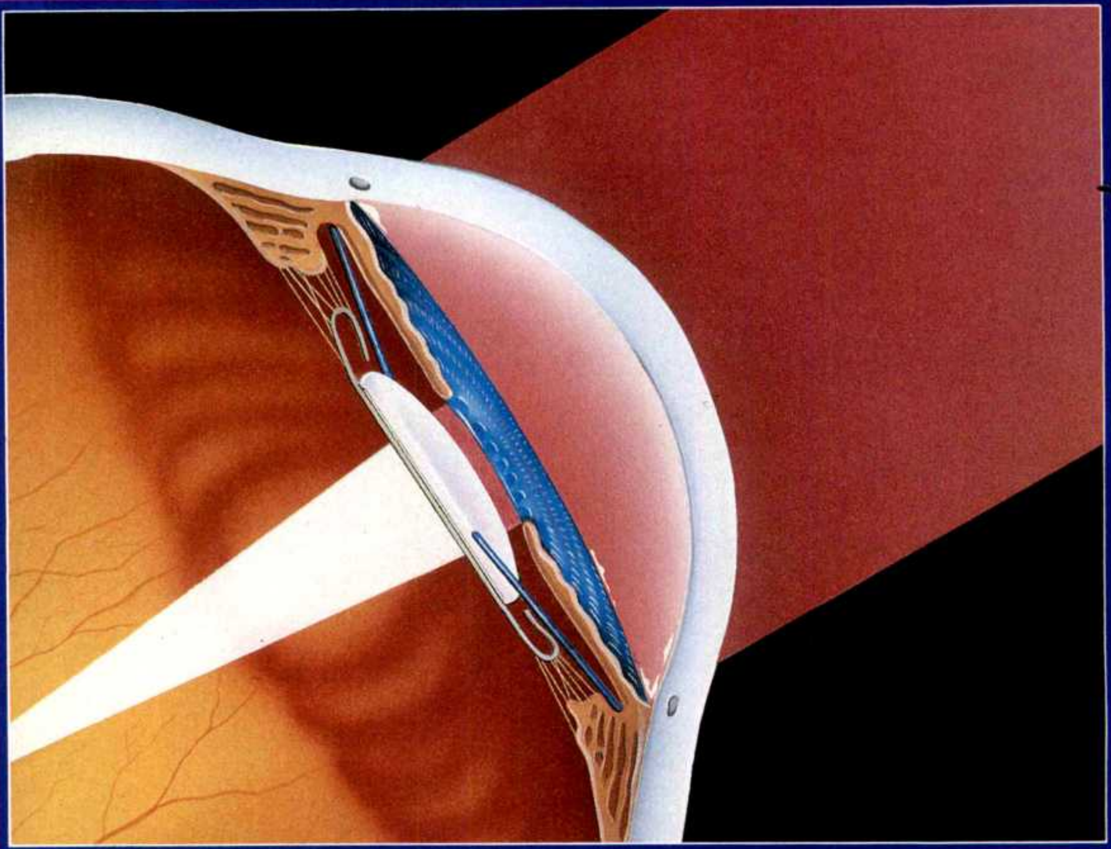

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Surgical treatment of superior bullous rhegmatogenous retinal detachments

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SUMMARY The results in 90 patients with superior bullous rhegmatogenous detachments operated on over a period of 10 years are presented. In only 70% of cases treated by scleral buckling, with or without drainage of subretinal fluid, was retinal reattachment achieved with a single operation. More recently the treatment of patients by external drainage, air injection into the vitreous cavity, and subsequent buckling has improved the success rate to 96%. It is suggested that the latter method be the surgical treatment of choice in such cases.

The use of non-drainage procedures, introduced by Custodis[1] and popularised by Lincoff and Kreissig,[2] makes a retinal detachment repair an entirely extraocular procedure. This procedure becomes difficult when deep subretinal fluid (SRF) is present between the detached retina and the pigment epithelium. Wide separation between the retinal layers inhibits accurate localisation of retinal holes and makes the application of cryotherapy difficult to judge. These difficulties often necessitate external drainage of SRF with its attendant risks.[3] The depth of SRF may be decreased either by preoperative posturing[4 5] or by immobilisation of the globe by surgical means.[6 7] In most cases treated by preoperative posturing such settling back does not occur, and the surgeon is then confronted with the problem of deep SRF at the time of operation. We have varied the surgical approach to these cases over the last 10 years and report our experience in the management of 90 cases.

Materials and methods

A consecutive series of 1050 patients admitted for retinal detachment surgery between 1974 and 1984 was studied. All patients had a full preoperative assessment with binocular indirect ophthalmoscopy, scleral depression, and three-mirror gonioscopy. Although this study was retrospective, at the time of examination particular attention had been paid to the depth of SRF between retinal holes and the pigment epithelium. The detachment was defined as bullous if no part of the retinal hole could be approximated to the underlying pigment epithelium by scleral indentation either preoperatively or at the time of operation. In all cases studied the hole(s) lay above the horizontal meridian. Details of preoperative findings, surgical technique, and postoperative course were entered on a proforma sheet for each case. Visual acuity and the anatomical state of the retina were assessed during postoperative visits; follow-up ranged from six months to eight years. Excluded from consideration were those patients in whom the detachment had been present for more than six months, in whom a giant tear or dialysis were present, or in whom there was evidence of widespread periretinal membrane formation.

SURGICAL METHODS

Over the 10 years of the study patients with bullous detachments were treated in one of three ways. In all cases scleral buckling was performed, either with a Silastic sponge as a local radial or circumferential implant, or with a silicone rubber band if encirclement was deemed necessary. Initially conventional buckling surgery with or without external drainage or subretinal fluid was performed. More recently external drainage has been combined with the intravitreal injection of air prior to cryotherapy and buckling. In this method, after external drainage of SRF, approximately 2 ml of air was injected via the pars plana into the vitreous cavity by a freely running syringe with a 27 gauge needle To encourage the production of a single bubble of air the eye was rotated prior to injection so that the injection site was at the uppermost part of the globe. After identification of the tip of the needle in the vitreous cavity

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the injection was begun, and it was continued (under indirect ophthalmoscopic observation) until the detached retina was seen to be approximated to the underlying pigment epithelium. The sclerotomy used for SRF drainage was then closed and cryotherapy and scleral buckling carried out. Postoperatively those patients who had had air injected were positioned in the head-down position for some days to avoid lenticular contact with the intravitreal air.[6]

Results

Ninety patients were found to have bullous retinal detachments as defined for inclusion in the study. Of the 90 cases 47 (52%) had non-drainage surgery, 18 (20%) external drainage and buckling, and 25 (28%) drainage, air injection, and buckling. Although the groups are not statistically comparable, we did not notice any obvious difference between them when age, refraction, and number of retinal holes were considered (Table 1). The duration of the retinal detachments also appeared to be similar in the three main groups (Table 2). The results of the individual procedures are summarised in Table 3.

NON-DRAINAGE AND BUCKLING

Of the 47 patients treated in this way the retina reattached with one procedure in 34 (72%). The reasons for failure of the initial procedure are shown in Table 4, and it may be seen that inaccurate localisation of the buckle was the cause in the majority of cases (11 of 13). One patient had an undetected retinal hole and another developed severe periretinal membranes.

EXTERNAL DRAINAGE OF SRF COMBINED WITH BUCKLING

Of the 18 patients treated in this way the retina was reattached with one procedure in 12 (66%). The remaining cases all failed because of inaccurate placement of the buckle

EXTERNAL DRAINAGE OF SRF, INTRAVITREAL AIR INJECTION, AND BUCKLING

Of the 25 patients in this group the retina failed to become reattached with one procedure in only one (4%). and this was also associated with inaccurate localisation. This patient went on to develop preretinal membranes, and the retina remained detached at six months (Table 5). No serious complications were encountered as a consequence of intravitreal injection.

Visual acuities and the anatomical state of the retina at six months are shown in Table 5. There is no obvious difference between the three groups in terms of visual acuity In both cases where the retina

Table 1 *Preoperative factors*

	Non-drainage	*External drainage*	*Drainage and air*
Age of patients			
0–50	6 (13%)	2 (11%)	5 (20%)
51–70	41 (87%)	16 (89%)	20 (80%)
Refraction of patients			
Emmetropic	14 (30%)	7 (39%)	11 (43%)
Myopic	25 (53%)	8 (44%)	11 (43%)
Aphakic	8 (17%)	3 (17%)	3 (14%)
Number of holes present			
Single	31 (66%)	10 (55%)	10 (40%)
Multiple	16 (34%)	8 (45%)	15 (60%)

Table 2 *Duration of detachment*

	Non-drainage	*External drainage*	*Drainage and air*
Less than one week	22 (47%)	7 (39%)	10 (40%)
One to four weeks	20 (43%)	8 (44%)	13 (52%)
One to six months	5 (10%)	3 (17%)	2 (8%)

Table 3 *Results of surgery*

	Non-drainage	*External drainage*	*Drainage and air*
Flat with one procedure	34 (72%)	12 (66%)	24 (96%)
Reoperation	13 (28%)	6 (33%)	1 (4%)
Total	47	18	25

Table 4 *Reasons for failure of initial operation*

	Non-drainage	*External drainage*	*Drainage and air*
Inaccurately placed indent	11	6	1
Undetected hole	1	—	—
Periretinal membrane	1	—	—

Table 5 *Results at six months*

	Non-drainage	*External drainage*	*Drainage and air*
Visual acuity at six months			
6/5 to 6/18	18 (38%)	6 (33%)	9 (36%)
6/24 to CF	21 (45%)	8 (44%)	15 (60%)
Less than CF	8 (17%)	4 (22%)	1 (4%)
Anatomical results			
Flat	46	18	24
Detached	1	—	1
Total	47	18	25

CF=counting fingers

remained detached the cause was preretinal membrane formation.

Discussion

The non-drainage procedure with its outstanding advantage of avoiding intraocular complications has been found to result in a high incidence of failure (13 out of 47 cases) when applied to superior bullous retinal detachments. This is mainly due to failure accurately to localise the buckle and thus close the retinal hole. There is also risk associated with the application of cryotherapy. If neuroepithelial whitening is used as the end point of cryotherapy, excessive freezing may occur in the presence of highly detached retinal holes. Such freezing has been implicated in postoperative complications.[9,10] Conversely, if lesser amounts of cryotherapy are used, so that only choroidal and retinal pigment epithelial blanching is produced, not only does visualisation of the freeze become difficult through a bullous detachment, but also the lesion produced will affect only the pigment epithelium, and this may jeopardise the tensile strength of the intraretinal adhesion.[11] To overcome these combined problems the height of the detachment must be reduced either by preoperative immobilisation of the globe or by external drainage of SRF at the time of surgery. Particular difficulties are encountered after external drainage of SRF when a highly detached retina is present. As the retina settles back, it tends to become folded. Much folding makes accurate localisation of retinal holes difficult and has resulted in a high reoperation rate in this series in cases treated in this way (six out of 18 cases). These problems may be overcome by the intravitreal injection of air prior to localisation and buckling. Originally introduced in 1911,[12] this procedure has been advocated by many authors.[13-16] Air injection will replace detached retinas against the pigment epithelium accurately and without folds, and also counteracts the hypotony induced by drainage of large quantities of SRF. Air is relatively non-toxic, though it has been implicated in the formation of posterior subcapsular cataracts.[8] The main disadvantages of air injection within the vitreous cavity are the risks of lenticular or retinal damage due to misdirection of the tip of the needle, the inadvertent formation of multiple intravitreal bubbles that obscure the retinal view, and over-filling of the eye, which in turn may result in retinal incarceration at the drainage site of SRF or closure of the central retinal artery. The injections of air into aphakic eyes, while supported by some studies,[17] is not advised after an intracapsular cataract extraction, as there is a risk of air gaining access to the anterior chamber and obscuring the retinal view if such access is not prevented by an intact anterior hyaloid face.

In this study we found that conventional buckling surgery, with or without the drainage of SRF, results in an unacceptably high proportion (31%) of patients needing a further procedure, with its attendant risks. Since we have used the technique of injecting air after drainage and before localisation, the surgical success rate has increased to 96%, and we have found no evidence to suggest that the visual results are inferior by this method (Table 5). We believe that this improvement is due to the more accurate buckling of the retinal hole that this procedure allows. In superior bullous retinal detachments, if preoperative immobilisation of the eye does not achieve sufficient flattening of the detached retina to allow a non-drainage operation, then external drainage followed by intravitreal injection of air and subsequent localisation, cryotherapy, and buckling should be the method of choice.

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D-ACE surgical sequence for selected bullous retinal detachments

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SUMMARY Forty-five out of 50 selected retinal detachments were successfully reattached by the D-ACE surgical sequence, that is, initial drainage of subretinal fluid followed by air injection into the vitreous, transcleral cryopexy, and definitive scleral buckling. The D-ACE sequence is recommended for difficult bullous detachments as a simple, safe, and effective alternative to non-drainage techniques.

Experienced retinal surgeons report success rates of over 90% reattachment (after one or more procedures) in large series of heterogeneous retinal detachments treated by scleral buckling. Detachments resulting from single small breaks in the pre-equatorial region are especially easy to treat (usually by a non-drainage technique), while the advent of closed microsurgery combined with internal gas tamponade has substantially improved the prognosis for more difficult problems such as posterior breaks in high myopes. There remain, however, several types of retinal detachment which (i) pose special buckling problems, (ii) are not generally considered for closed microsurgery, and (iii) contribute disproportionately to failed surgery and subsequent development of proliferative vitreoretinopathy (PVR). Bullous detachments from multiple large equatorial breaks represent one such group, because the extensive buckling frequently results in fish-mouthing of the breaks. In 1980 a surgical sequence comprising initial subretinal fluid drainage (D), followed by intravitreal injection of air (A), transcleral cryopexy (C), and episcleral explant (E) —hence D-ACE sequence[1]—was introduced in order to overcome the problems which we had previously encountered in managing these difficult detachments. This report describes the details and advantages of the method, and presents the outcome in 50 consecutive procedures.

Material and methods

Between 1980 and 1984 50 eyes of 50 patients with bullous retinal detachment underwent surgery by the D-ACE sequence in the Surgical Vitreoretinal Unit at Moorfields Eye Hospital. Half the cases were operated on by the consultant-in-charge and the remainder by various members of the resident surgical staff. Eighteen of the 50 eyes had undergone one or more reattachment procedures previously. The majority (30 eyes) harboured multiple, usually equatorial, retinal breaks. Of the remainder nine eyes had single tears deemed unsuitable for non-drainage surgery by virtue of their large size and equatorial location, gross elevation, associated static traction, or a combination of these factors; four eyes had large elevated equatorial holes in the outer leaf of a retinoschisis complicated by retinal detachment; two eyes had 90° dialyses showing fishmouthing after previous buckling; two eyes had no clearly identifiable breaks preoperatively or at surgery; and three eyes had both peripheral and posterior breaks (a macular break in two eyes and a paramacular tear in one eye). Five eyes had signs of early PVR, and two eyes had retinal incarceration from previous surgery, four eyes were aphakic (two with intraocular lenses). Apart from one eye with retinal dialysis and one with retinoschisis the retinal detachments were all associated with posterior vitreous detachment.

Patients were operated upon under general anaesthesia without nitrous oxide; the anaesthetist was encouraged to hyperventilate the patient to promote choroidal vascular constriction. A subconjunctival

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injection of Mydricaine (atropine, procaine, adrenaline, boric acid, sodium metabisulphite) was given to ensure maximal pupillary dilatation throughout the procedure. After reflection of conjunctiva and Tenon's capsule in quadrants to be treated the recti were secured with loops of 2/0 silk.

DRAINAGE OF SUBRETINAL FLUID

Subretinal fluid was usually drained just above or below one of the horizontal rectus muscles at the equator. After cautery of the lips of a partial-thickness meridional sclerotomy (thus creating a scleral cloaca), the incision was deepened to bare choroid which was lightly cauterised and a mattress suture of 5/0 Ethibond placed through the lips of the sclerotomy. The choroid and Bruch's membrane were then perforated with a sharp 24 gauge needle, and 1–3 ml of subretinal fluid was milked from the globe by intermittent scleral depression while the sclerotomy edges were kept everted and extracted from the globe contour (with consequent prevention of retinal incarceration). The sclerotomy was then securely closed.

INTRAVITREAL INJECTION OF AIR

Before drainage of the subretinal fluid, air or a mixture of air and sulphahexafluoride (SF6) 20–80% was drawn up via a Millipore filter into a 5 ml syringe; in three eyes the volume to be injected was less than 1 ml, so 100% SF6 was used. A site for injection was almost invariably chosen 3–4 mm from the limbus and mid-way between the superior rectus and medial rectus insertions, since this was the easiest site to keep 'high' while still affording internal visualisation by indirect ophthalmoscopy. Immediately following subretinal fluid drainage, and with the contour of the superonasal quadrant maintained by inferotemporal scleral indentation, the sclera and pars plana were penetrated by a 27 gauge needle attached to the syringe and observed in mid-vitreous by indirect ophthalmoscopy. The needle was then partially withdrawn to leave a 1–2 mm intravitreal penetration. Once the injection site was confirmed as being the highest point of the globe, gas was smoothly injected into the gel compartment as a single bubble while the scleral indentation was partially released (Fig. 1); multiple intraocular gas bubbles ('fish eggs') were thereby avoided. The needle was then completely withdrawn once it had been ascertained that the eye remained slightly hypotonic so as to preclude any prolapse of vitreous gel through the injection site (which might otherwise result in distortion of tears) and also to leave space for the scleral buckle.

TRANSCLERAL CRYOPEXY

With the exception of the two full-thickness macular breaks, all retinal breaks were completely surrounded by multiple focal cryoapplications, particular care being taken to treat anteriorly up to the ora serrata in the case of large horseshoe breaks. The iceball was allowed to develop so as to freeze both the pigment epithelium and reapposed neural retina, but overtreatment (potentially aggravated by the thermal insulating effect of the adjacent gas bubble) was avoided by careful ophthalmoscopic monitoring and the rapid defrost capability of the MIRA or Wallach cryoprobes. Cryopexy was also applied

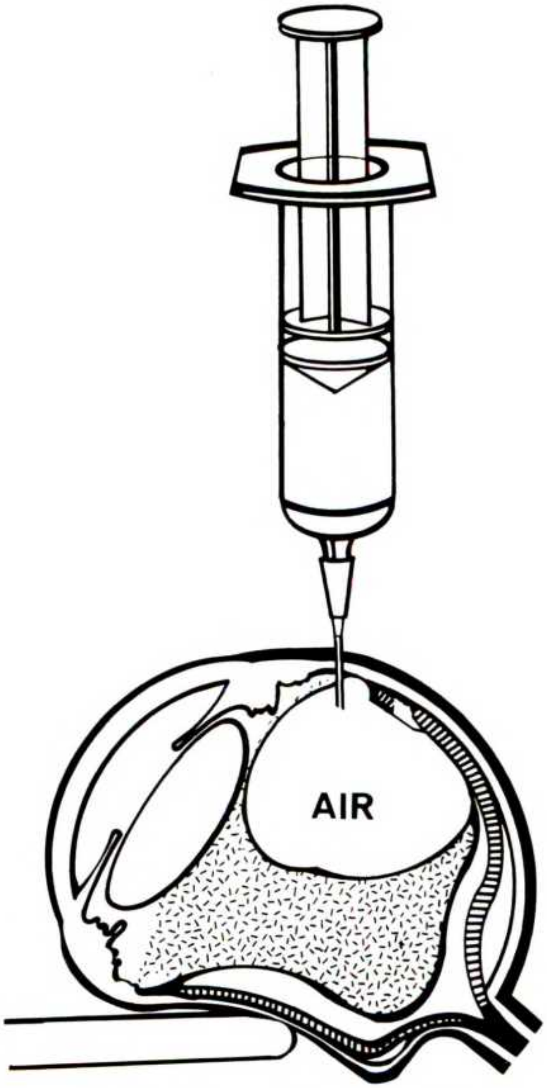

Fig. 1 *Needle-tip-high method of intravitreal air injection (after Norton).*

across the posterior margin and lateral edges of other vitreoretinal adhesions—for example, lattice and snail track degeneration—but cryopexy of the subretinal fluid drainage site was avoided wherever possible.

EXPLANT PLACEMENT

With the exception of the posterior polar breaks in three eyes all retinal breaks were covered externally and indented from their posterior limit up to the ora serrata by means of a 'break-ora occlusive buckle'. This was usually accomplished circumferentially by means of a thin piece of solid silicone material (most frequently a 279 tyre) whose width was chosen (or fashioned) so as to create a gentle (1 mm) indentation of the sclera by means of hemi-Halsted mattress sutures, each comprising a short (3 mm) circumferential bite 4 mm behind the localisation mark of the posterior limit of the most posterior tear, and two radial bites anteriorly through the lateral expansions of the rectus muscle insertions or the intervening scleral ring. The limited height of buckling was controlled by careful matching of suture spread with buckle width and by suture tightening against a well formed globe (by virtue of the gas reconstitution and scleral counter-depression at the start of buckle indentation). The extent of circumferential buckling varied from 60° to 360° (mean 170°) of the ocular circumference. In three eyes equatorial or postequatorial breaks were mounted on a radially orientated Silastic sponge explant and in four further eyes small postoral breaks were closed by part of a pre-equatorial encircling 240 band. In 30 eyes an encircling band was used in conjunction with a tyre, and it was otherwise fixed by mattress sutures either across the posterior border of the vitreous base (posterior scleral bite 12 mm from the limbus) or more posteriorly in the presence of equatorial lattice lesions. The tension in the strap was adjusted via a Watzke sleeve to achieve a low (1 mm) scleral indentation.

The central retinal artery was then checked, and, if it was closed, an anterior chamber paracentesis was performed or excess gas was tapped off by re-elevating the superonasal quadrant and reinserting the 27 gauge needle (closed by means of a finger over the Luer fitting but momentarily reopened once the needle was positioned within the gas bubble). Tenon's capsule was then sutured over the explants to reconstitute the intermuscular septum and the conjunctiva closed. Subconjunctival betamethasone 4 mg and cephaloridine 125 mg were routinely injected.

Postoperatively the patient was positioned so that the arc of contact of the gas bubble included as many of the breaks as possible, and this was maintained for 2–6 days. The minimum follow-up interval after surgery was six months.

Results

RETINAL REATTACHMENT

The retina reattached either completely or virtually completely in the immediate postoperative period; in two elderly patients residual inferior subretinal fluid did not become absorbed for two weeks. Transient redetachment occurred on the second postoperative day in two eyes and was attributed to reopening of a break from displacement of the air bubble into the retrohyaloid space.

In 45 eyes retinal reattachment was maintained throughout the follow-up interval and, with a single exception (see below), was associated with visual improvement. The extent of visual recovery reflected the duration of macular detachment, the predetachment acuity, and the age of the patient. The retina became detached again in five eyes, two of which were not reoperated upon. Reoperation (involving vitrectomy, internal gas tamponade, and rebuckling in two eyes, and rebuckling alone in one eye) resulted in successful and permanent reattachment in the other three eyes. Thus retinal reattachment was achieved in 90% of eyes by means of the D-ACE sequence (subsequently improving to 96% after reoperation).

COMPLICATIONS

Significant haemorrhage occurred during surgery in six eyes. In two eyes undergoing reoperation soon after failed cryopexy and buckling, localised subretinal haemorrhage occurred at the time of drainage of subretinal fluid, and a further eye had mild subretinal bleeding from a perforating buckle suture. In one eye a choroidal haemorrhage followed cryotherapy to the site of subretinal fluid drainage adjacent to a large tear; this prevented the completion of cryocoagulation of the tear, which reopened three weeks after initially successful surgery. Finally, two highly myopic eyes developed a choroidal haemorrhage distant from the subretinal fluid drainage site after extensive cryopexy to multiple tears and lattice lesions; the retina reattached in both cases, but in one there was no associated visual improvement.

Serous ciliochoroidal effusions were noted in eight eyes during the first two weeks postoperatively but all settled spontaneously. Transient signs of anterior segment ischaemia, including shallowing of the anterior chamber and folds in Descemet's membrane, were noted in five eyes but required no specific treatment. Each of the following complications occurred once in the series: minimal retinal incarceration requiring no treatment; progressive posterior subcapsular lens opacities a year after surgery (and conceivably attributable to gas/lens contact); lens touch from paracentesis causing cataract; and macular pucker. The only eyes to show widespread evidence of PVR were those two eyes in which the retina became redetached and were not reoperated upon.

Discussion

Successful management of rhegmatogenous retinal detachment demands both identification of all causative retinal breaks and their subsequent closure. Internal closure of breaks by air tamponade per se, as popularised by Rosengren,[2] may be effective but often only temporarily if there is persistent traction on the breaks (as with horseshoe tears). Chawla *et al.* reported good results using cryopexy followed by drainage of subretinal fluid, air injection, and equatorial encirclement,[3,4] but many of the detachments might have been readily treated by local scleral buckling without drainage of subretinal fluid. The gratifying results of surgery for the problematic detachments in this series are partly attributable to the employment of definitive explants as opposed to equatorial encirclement, which seldom closes the anterior horns of large horseshoe tears effectively. Furthermore, the use of low-profile buckles (which the associated gas tamponade permits) minimises the discomfort, ischaemia, and astigmatism[5] which so often accompany the high buckles required for non-drainage surgery. Low-profile buckles also reduce the degree of fishmouthing of breaks, and, while fishmouthing is an inevitable complication of extensive buckling for multiple large equatorial breaks, no recourse to special buckling methods[6] is necessary.

The D-ACE sequence of achieving combined buckling and internal tamponade has a number of theoretical advantages, the validity of which have been born out in practice. The chief complication of subretinal fluid drainage—haemorrhage from the perforation site—is not so much influenced by the site and technique of perforation as by its timing during the course of the surgical procedure. Choroidal vascular congestion induced by cryotherapy renders perforation especially hazardous late into the operative procedure.[7] Thus drainage of subretinal fluid as the first step in the surgery substantially reduces this risk. Furthermore, provided the introduction of a single large intravitreal gas bubble is successfully accomplished,[8] no problem arises in visualising and localising the breaks, which can then be optimally treated by cryotherapy. In order to maximise the benefits of internal gas tamponade while minimising complications, therefore, the decision to forgo non-drainage surgery has to be made preoperatively rather than during the course of the surgical procedure.

The D-ACE surgical sequence has filled a significant gap in our range of surgical options for rhegmatogenous retinal detachment between a non-drainage technique and the employment of vitrectomy—for example, for posterior breaks and for established PVR. When treating difficult detachments which require extensive cryotherapy, we believe that the risk of delayed, incomplete, or failed closure of coagulated breaks after non-drainage surgery poses a greater threat of subsequent PVR than the risk of including the drainage of subretinal fluid in the procedure, as in D-ACE sequence. Not only has the D-ACE sequence improved our success rate for difficult detachments, it has also had a notable effect in reducing subsequent PVR.

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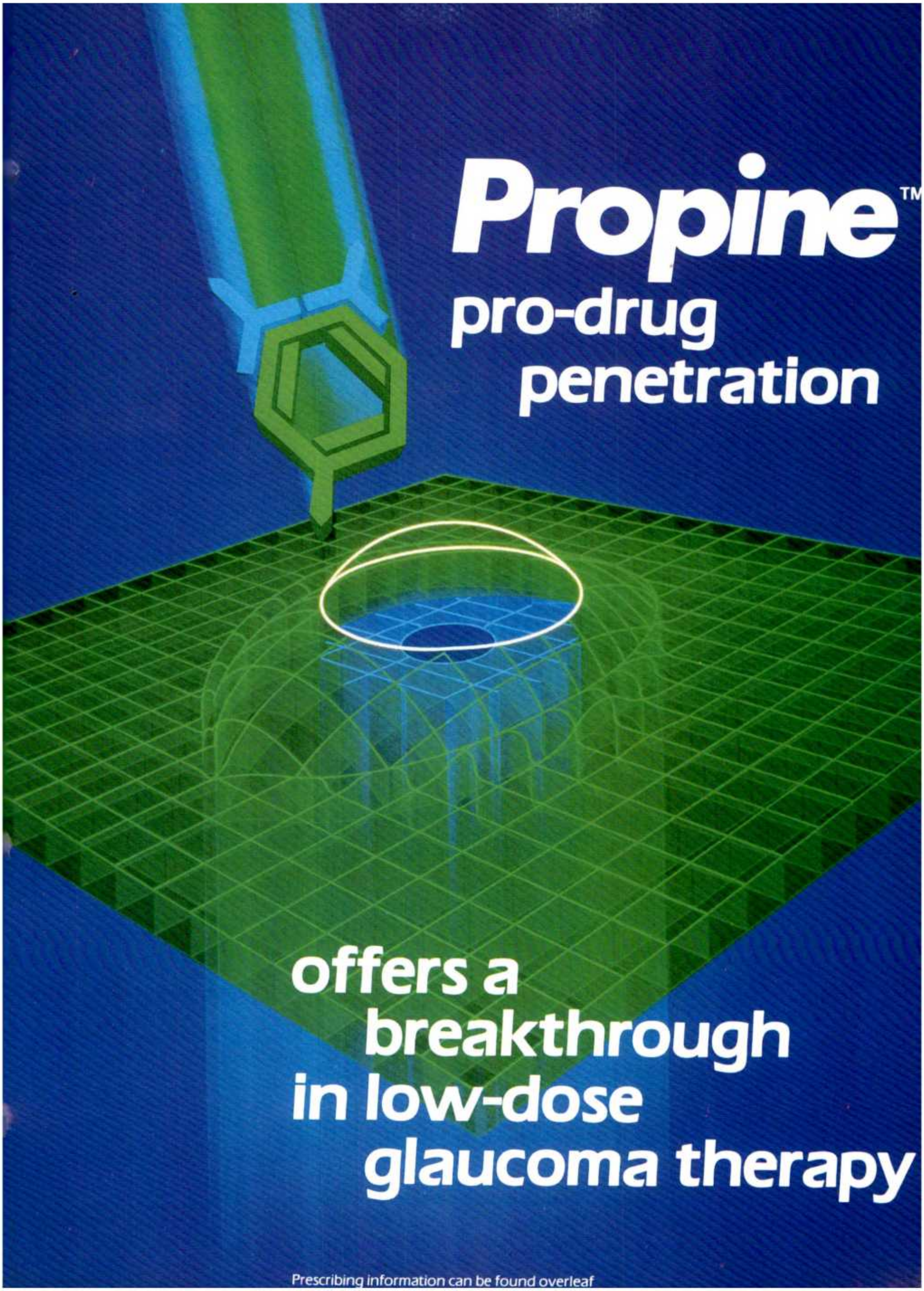

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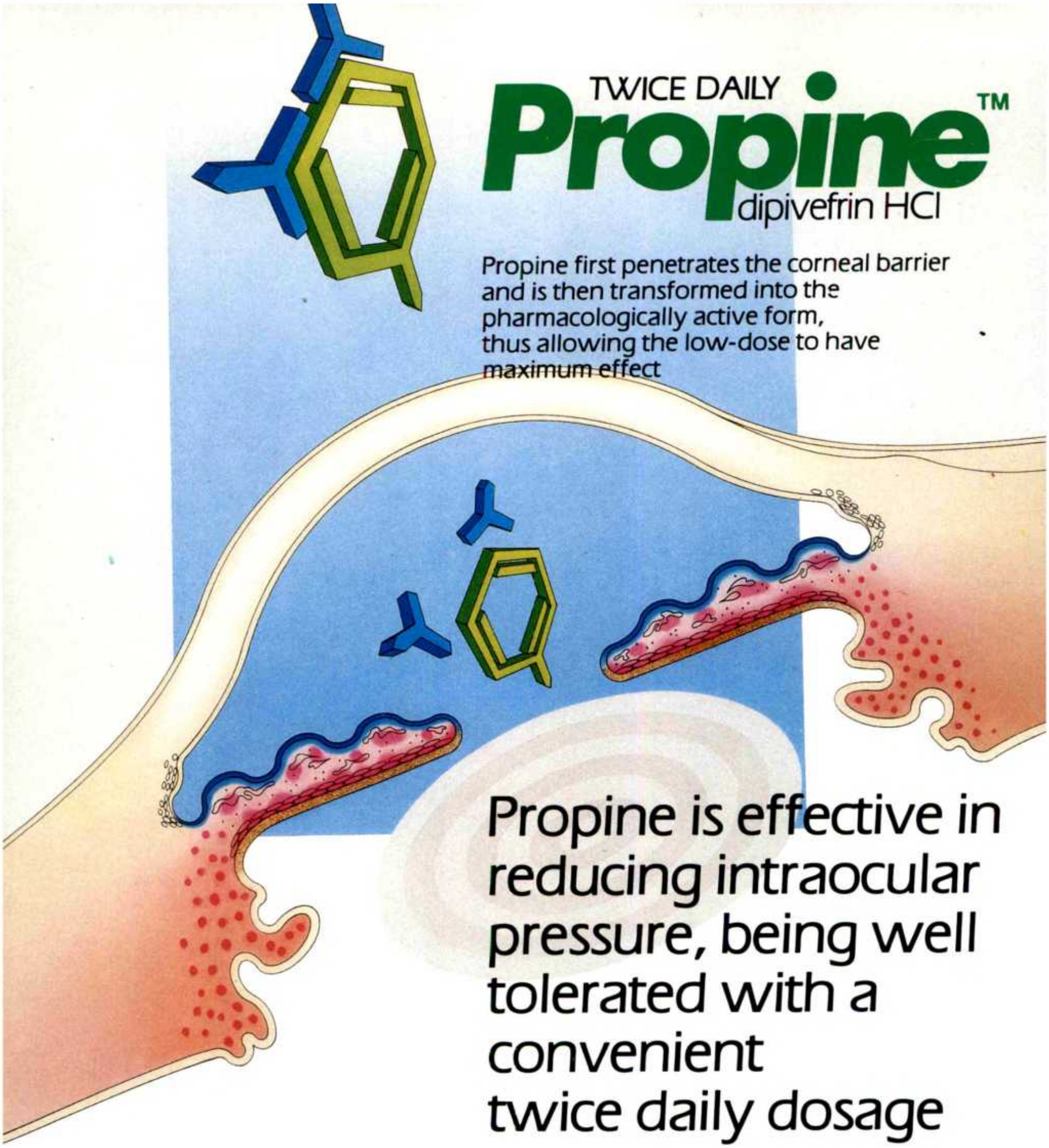

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Aphakic retinal detachment

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SUMMARY A study of 132 cases of aphakic retinal detachment (ARD) following mainly intracapsular cataract surgery has been made. Forty-nine cases (37%) were found to have vitreous incarcerated into the cataract section out of a total of 54 (41%) cases who had suffered a vitreous complication during cataract surgery. A study of the characteristics of ARD reveals that those cases having had a vitreous complication in the management of their cataracts are more likely to develop detachment within three months than those not suffering from such a complication. The occurrence of these early post-extraction retinal detachments is not influenced by the presence of underlying axial myopia. When we compared ARD in patients whose cataract extractions had been complicated by vitreous incarceration with those ARDs following uncomplicated cataract surgery, we found that the characteristics of the detachments were very similar. Thus distribution of underlying myopia, extent of detachment, length of time of detachment, and multiplicity and type of retinal holes were generally similar. However, ARD following complicated cataract surgery is more likely to suffer from periretinal fibrosis. The findings confirmed the risk of ARD following complicated intracapsular cataract surgery and support the tendency to perform the extracapsular operation.

The surgery of aphakic retinal detachment (ARD) has gained a reputation for difficulty because the retinal holes are often hard to find and, in comparison with phakic retinal detachment, ARD progresses more rapidly and has a more pronounced tendency to periretinal fibrosis.[1 2] In most studies of ARD little attention has been paid to the coincident clinical findings in the anterior segment or to relate these findings to observations made in the posterior segment. In an attempt to reduce the incidence of ARD, the surgeon operating on the anterior segment has at times varied his approach to the removal of the crystalline lens. In extracapsular techniques in which surgery is followed by capsulotomy the incidence of ARD is not lower than in the intracapsular approach.[3 4] However, recently there has been renewed interest in the methods of extracapsular extraction, and in techniques where the posterior capsule is preserved ARD is less likely to occur.[5-8]

It is clear that changes in the anterior segment as a consequence to the cataract operation will be related to those subsequently occurring in the posterior segment. In this study we have tried to evaluate these events by studying both anterior and posterior segments in a group of patients suffering from ARD, with particular emphasis on comparing ARD after uncomplicated extractions with ARD following complicated cataract extraction. We also studied for comparison a group of patients who underwent cataract surgery and who did not develop retinal detachment.

Material and methods

Two groups of patients were studied.

(1) ARD group. One hundred and thirty-two consecutive cases of ARD seen in the Retinal Clinic at St Thomas's Hospital were examined. Information about these patients was gathered prospectively from proforma sheets filled in at the time of detachment surgery. Every patient was examined by indirect ophthalmoscopy and scleral depression with slit lamp biomicroscopy and three-mirror contact lens. Information was recorded on colour coded charts. Particular attention was paid to the cataract section using gonioscopy, noting the presence of not of vitreous in the anterior chamber and whether or not there was incarceration of vitreous into the cataract section. When possible, the records made at the time of cataract surgery were checked with particular regard to recorded vitreous loss. ARD cases subsequent to

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cataract surgery following trauma or following the surgery of congenital cataract surgery were excluded.

(2) Cataract group. The anterior segments of 200 eyes (146 patients) not complicated by subsequent retinal detachment were examined. These cases were as nearly consecutive as possible, exceptions being those patients who were unable to attend for examination. All these cases had their cataract surgery more than one year prior to the examination.

Results

TYPE OF CATARACT EXTRACTION

In both cataract and ARD groups there was a high incidence of intracapsular cataract extraction. In the ARD group of 132 eyes 126 had had intracapsular extraction and six had had extracapsular extractions. In the latter cases two subsequently had had a substantial posterior capsulotomy performed. In the cataract group 196 eyes had intracapsular operations and only four had extracapsular operations (none of these had had posterior capsulotomy).

VITREOUS LOSS AND VITREOUS INCARCERATION

ARD group. Of 132 ARD cases 31 (23%) suffered recorded vitreous loss at the time of cataract surgery. Of these 31 patients we found that only five had absence of vitreous from the cataract section. The remaining 26 were found to have a varying extent of vitreous incarceration into the cataract wound. We also found an additional 23 cases where vitreous was incaracerated into the section in spite of apparently uneventful cataract surgery. A total of 49 cases (37% of the total ARD group) therefore had incarcerated vitreous into the section, which, with the additional five cases of recorded vitreous loss, where vitreous had been freed from the section, meant that a total of 54 ARD patients (41%) had suffered a vitreous complication in their management.

Cataract group. In the group of 200 cases 17 were recorded as having lost vitreous at surgery. When we examined these 17 patients, seven were found to have vitreous incarceration into the section. A further 10 cases were found to have vitreous in the section after what was recorded as uncomplicated surgery. Thus of 200 cataract patients, an unexpectedly high number of 27 were found to have a vitreous complication in their management (13·5%), and 17 of these still had vitreous in the section (8·5%). It is well known that to leave vitreous incarcerated in the section at the end of surgery is undesirable, as an unacceptably high proportion of these cases fare badly.[9] Our findings showed that, of the 17 patients in whom vitreous loss had been recorded, in only 10 was the clearance of vitreous from the wound adequate. In a further 10 cases vitreous incarceration into the wound was not recognised at all, though it is possible that in some cases vitreous may have become adherent to the cataract section in the postoperative period.

The cataract and the ARD group are not statistically comparable, but the difference in vitreous complications between the two groups suggests the importance of this event in promoting aphakic retinal detachment.

CHARACTERISTICS OF THE ARD GROUP

Sex. We confirmed the previously reported[2 3 10] proclivity for ARD to affect males. Out of 111 patients 69 were male and 42 were female.

Age. The ages in the ARD group ranged from 48–91 years with a peak incidence in the 60–70-year age group. These ranges were consistent with those of other studies.[1 2]

Refractive state. This was deduced by similar methods and definitions as those used by previous workers.[5 11 12]

Myopia and vitreous complication. Of the 54 ARD patients who suffered a vitreous complication 19 (35%) were previously myopic. In the 78 ARD cases that were not associated with a vitreous complication 37 (49%) were myopic. Thus there was no tendency for the vitreous complication group to contain relatively more myopes.

We compared the characteristics of aphakic retinal detachments whose cataract extractions had been complicated by a vitreous event with those in which no such complication had occurred. We studied the interval between the cataract extraction and the presentation of the retinal detachment, the duration of the retinal detachment at the time of retinal surgery, the characteristics of the retinal holes, the extent of the detachment at the time of presentation, and the presence of periretinal fibrosis.

Interval between the cataract extraction and the onset of retinal detachment. Among the 54 ARD cases whose cataract extraction had been complicated by a vitreous complication 22 (42%) detachments occurred within three months after extraction (we called this early ARD). Of the 78 patients with ARD whose cataract operation had not been complicated by vitreous event only 8 (10%) suffered retinal detachment within three months of extraction. These findings (Figs. 1 and 2) show that the risk of early detachment significantly increases ($p<0·01$) in those patients who have had a vitreous complication in their cataract surgery. This confirms the finding of a previous study.[13]

Underlying myopia and early ARD. In the 54 cases of ARD following complicated cataract extraction there were 19 with underlying myopia and 35 without underlying myopia. Among the latter 35 cases 14 (39%) became detached within three months. Of the

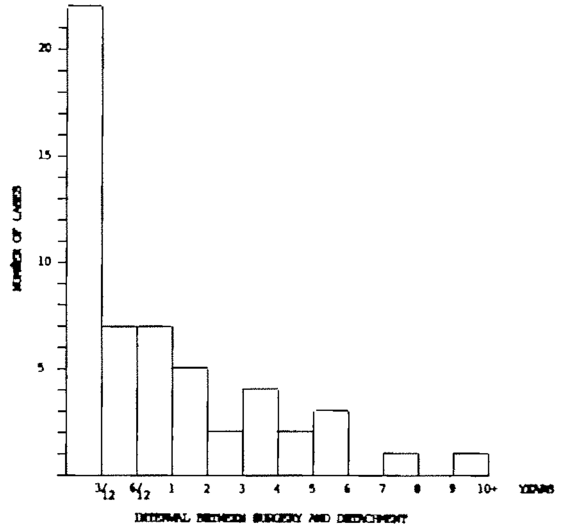

Fig. 1 *ARD following complicated cataract surgery.*

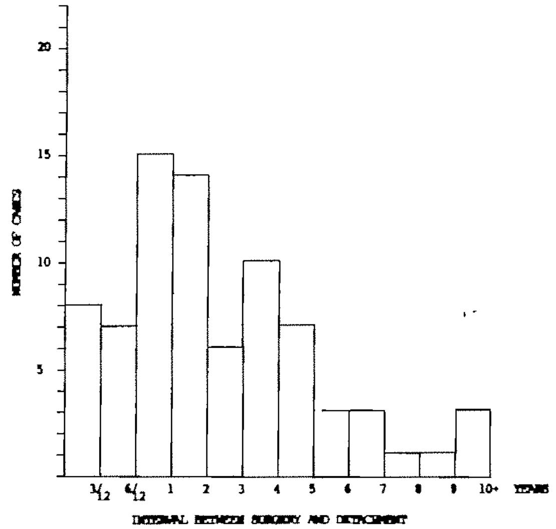

Fig. 2 *ARD following uncomplicated cataract surgery.*

19 cases with underlying myopia eight (42%) became detached within a similar period. The difference between the two groups is not statistically significant ($p>0{\cdot}05$) and shows that detachment within three months (early ARD) is not influenced by underlying myopia.

Extent of detachment. Table 1 shows that there was no difference in the extent of the detachment between those patients with ARD who suffered a vitreous complication in the management of their cataract extraction and those who had not suffered this complication ($p>0{\cdot}05$).

Table 1 *Extent of detachment at presentation in 132 ARDs*

Group	*1–2 quadrants detached*	*More than 2 quadrants detached*
ARD following complicated cataract extraction (54 eyes)	21 (39%)	33 (61%)
ARD following uncomplicated cataract extraction (78 eyes)	35 (45%)	43 (55%)

Table 2 *Duration of detachment at time of surgery in 132 ARDs*

Group	*Less than 1 month*	*More than 1 month*
ARD following complicated cataract extraction (54 eyes)	24 (44%)	30 (56%)
ARD following uncomplicated cataract extraction (78 eyes)	30 (39%)	48 (61%)

Length of time of detachment. Table 2 shows that there was no difference between the length of time of detachment between those patients with ARD who suffered a vitreous complication during their cataract extraction and those who had not suffered this complication ($p>0{\cdot}05$).

RETINAL HOLES

Multiplicity of holes (Table 3). Among the cases of ARD following complicated cataract surgery there were 16 where the retinal holes were multiple. In only two of these were more than two holes found, and in no case was a retinal detachment characterised by a multiplicity of holes widely separated in detached retina. Among ARD cases following uncomplicated cataract surgery there were 23 with multiple holes. In 19 of them holes were found in one quadrant of the retina, and in only four were the holes widely separated. Thus even in uncomplicated ARD cases the so-called typical aphakic detachment[14 15] characterised by multiple holes was rarely seen. Failure to detect retinal holes was similar in the two groups.

Periretinal fibrosis. Periretinal fibrosis ranged in severity from early periretinal membrane formation to massive proliferative vitreoretinopathy and was

Table 3 *Number of retinal holes*

Group	*Single*	*Multiple*	*Nil*
ARD following complicated cataract extraction (54 eyes)	76 (48%)	16 (30%)	12 (22%)
ARD following uncomplicated cataract extraction (78 eyes)	35 (45%)	23 (29%)	20 (26%)

Table 4 *Results of surgery*

	Success	*Failure*
	114 (86%)	*18 (14%)*
ARD following complicated cataract extraction (54 eyes)	46 (85%)	8 (15%)
ARD following uncomplicated cataract extraction (78 eyes)	68 (87%)	10 (13%)

found in some degree in 51 (39%) of the 132 ARD cases. Periretinal membranes were found to have formed in 32 of the 54 cases (59%) of ARD whose cataract had been associated with vitreous complications. But they were found in only 19 out of 78 cases (24%) of ARD whose cataract extractions had been uncomplicated. This difference is significant ($p<0{\cdot}01$). It should be noted that we had found that the length of time of the detachment (a factor contributing to periretinal fibrosis) was not significantly different between the two groups (Table 2). Thus cases of ARD associated with periretinal membranes are more likely to occur if the ARD had followed a complicated cataract operation.

RESULTS OF SURGERY

Successful treatment was defined as achievement of a flat retina, and the shortest follow-up period has been one year. This was obtained in 114 cases (86%), as seen in Table 4. It can be seen that the anatomical results of surgery in both groups of ARD are almost identical.

Discussion

Even though we found vitreous adherent to the cataract section in 8·67% of cases of cataract operations not complicated by subsequent retinal detachment, the finding that 49 cases (37%) of our total series of 132 ARDs had vitreous incarcerated into the section, and that 54 (41%) cases had suffered a vitreous complication during the management of their cataract surgery, confirms that this is a complication of importance in promoting events leading to subsequent retinal detachment. Forward movement of gel following intracapsular lens extraction to fill the space previously occupied by the lens not only encourages posterior vitreous detachment if not already present at the time of surgery[10 16 17] but, by filling the space previously occupied by the crystalline lens, effectively increases the volume of the vitreous cavity and results in increased capacity for excursion of the gel when it moves. This in turn results in greater dynamic traction[18] at the posterior border of the vitreous base following vitreous detachment than exists in the phakic eye. Our findings indicate that incarceration of gel into the cataract section greatly increases the risk of retinal detachment in the aphakic eye following intracapsular extraction. It seems that this anterior incarceration alters the nature of the posterior vitreous detachment, tending to increase dynamic traction at the posterior border of the vitreous base in these cases. We were somewhat surprised to find there was little difference in the morphological characteristics of the type of retinal detachment in those aphakic retinal detachments following cataract surgery associated with vitreous complications and those following uncomplicated cataract surgery. Thus there was similarity in the extent of the detachment, the duration of the retinal detachment, and the type and position of the retinal holes, but there was a greater tendency to early detachment and to periretinal membrane formation in ARD following cataract surgery associated with vitreous complication.

The pathogenesis of ARD following intracapsular cataract surgery is probably multifactorial, and our concentration on vitreous events in the anterior segment does not discount the importance of other associated factors that may be contributing—for example, myopia and lattice degeneration. Unlike these other factors, however, the removal of cataract is under surgical control, and this study indicates that the intracapsular cataract operation carrying with it the risk of vitreous complications strongly predisposes the eye to early ARD if these complications occur. We do not have enough information to know if proper management of vitreous loss by removing vitreous from the section will reduce the risk of aphakic detachment in these cases.

This study gives weight to the growing popularity of extracapsular cataract surgery, which preserves the integrity of the posterior segment.

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Ectopic intracranial retinoblastoma in childhood

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SUMMARY Twelve out of a series of 630 children with retinoblastoma, treated in the ocular oncology units at St Bartholomew's and Moorfields Eye Hospitals during the past 30 years, have developed ectopic intracranial retinoblastoma. The ectopic tumour occurred in the pineal region in eight children and in the suprasellar region in four. Ten patients had bilateral retinoblastoma, one unilateral disease, and one child presented with an isolated suprasellar tumour but no evidence of retinal disease. The interval from the initial diagnosis of retinoblastoma to the development of ectopic intracranial disease ranged from 4 to 70 months, median 34 months. Methods of treatment for the ectopic tumour varied, but all 12 children died with a median survival of only 8 months following the diagnosis of ectopic retinoblastoma. Subsequent spread of tumour to other sites within the central nervous system proved to be the most frequent cause of death. Ectopic intracranial retinoblastoma is a potentially curable neoplasm, but it requires adequate therapy to the whole neuraxis as well as high dose equivalent radiotherapy to the primary tumour.

The problem of ectopic non-metastatic retinoblastoma was first recognised by Jacobiec *et al.* in 1977.[1] Three years later Bader and colleagues,[2] used the term 'trilateral' retinoblastoma to describe the clinical syndrome of bilateral retinoblastoma with an ectopic midline intracranial tumour. These authors subsequently reported on 11 children with features characteristic of trilateral retinoblastoma and also included details of three children with either parasellar or suprasellar retinoblastoma.[3] They suggested that the development of an ectopic midline neuroblastic tumour in a patient with bilateral retinoblastoma represented an additional focus of multicentric retinoblastoma rather than a second primary tumour and drew attention to the ontogenesis of the pineal gland, likening the human pineal to a 'third eye'. They postulated that the retinoblastoma gene confers an increased susceptibility to the development of neuroblastic tumours which, although usually presenting in the retina, can occur in other intracranial sites, particularly in cells of photoreceptor origin. Photoreceptor morphology has certainly been identified in cases of pineoblastoma occurring without retinoblastoma,[4] and the suprasellar or IIIrd ventricular region is a well recognised site of origin for primary 'ectopic' pineoblastomas.[5]

In this report we describe the clinical presentation, treatment, and outcome of 12 children with ectopic intracranial retinoblastoma seen at St Bartholomew's and Moorfields Eye Hospitals during a period of 30 years. Three of the 12 cases summarised in Table 1 have been cited in previous reports—cases 4 and 5[3] and case 11.[6] We also discuss ways in which treatment might be modified in an attempt to improve the current dismal prognosis.

Material and methods

PATIENTS

Six hundred and thirty children with retinoblastoma presenting to St Bartholomew's and Moorfields Eye Hospitals during the period 1954 to 1983 have been followed up. There were 360 males and 270 females, a male to female ratio of 1·4:1. Four hundred and thirty two (69%) of the children had bilateral disease, reflecting selection in the referral pattern. Twelve of these 630 children developed ectopic intracranial retinoblastoma. The clinical presentation and treatment given for the initial retinoblastoma of these twelve children is set out in Table 1. There were eight girls and four boys. One child (patient 7), a younger sibling of patient 3, presented with an isolated suprasellar tumour but no evidence of retinal disease. The mother of the two siblings had bilateral retino-

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Table 1 *Characteristics of patients with ectopic intracranial retinoblastoma*

Patient no.	*Sex*	*Age at diagnosis of RB*	*Year of diagnosis of RB*	*Initial treatment of retinoblastoma*	*Interval between diagnosis of RB + ectopic tumour*
1	M	2/12	1954	Enucleation L eye + RT 16 Gy to L orbit, Co plaque to R eye	5 yr 8/12
2	M	8/12	1956	Enucleation L eye, Co plaque to R eye	2 yr 5/12
3	F	2/12	1969	PC L eye, PC R eye	4/12
4	F	2/12	1973	Enucleation R eye, PC + Cryo + RT 35 Gy to L eye	6 yr 8/12
5	F	1/12	1973	35 Gy to both eyes	6 yr 5/12
6	M	5/12	1974	Enucleation R eye, PC + Cryo L eye	3 yr 3/12
7*	F	5/12	1976	NA	NA
8	F	9/12	1977	Enucleation L eye, RT 36 Gy R eye	4 yr 7/12
9	F	2/12	1978	Enucleation R eye, RT 35 Gy L eye	2 yr 10/12
10†	F	14/12	1981	Enucleation R eye	1 yr 7/12
11	M	12/12	1982	Enucleation R eye	1 yr 2/12
12	F	3/12	1982	Enucleation L eye, RT 36 Gy R eye	1 yr 3/12

*Child with isolated suprasellar retinoblastoma and sib of patient 3.
†Child with unilateral retinoblastoma.
Co plaque = ^{60}cobalt plaque. RT = external beam irradiation. PC = xenon photocoagulation. Cryo = cryotherapy. NA = not applicable.

blastoma and developed a malignant melanoma as a second primary tumour at the age of 31 years. The father of the child with unilateral disease also had unilateral retinoblastoma.

Results

Ten of the 11 children with retinal involvement had bilateral disease diagnosed between the age of 1 and 12 months, median 2 months. Enucleation of the worst affected eye was carried out in eight children. The remaining eye was treated with a cobalt plaque in two children, external beam irradiation in four children, external beam with cryosurgery and xenon photocoagulation in one child, and xenon photocoagulation and cryosurgery alone in the remaining child. Of the two children who did not undergo primary enucleation one was treated with external beam irradiation to both eyes while the other received bilateral xenon photocoagulation. The child with unilateral disease (patient 10) was treated by enucleation alone. No child received chemotherapy.

There was no evidence of tumour involving the cut end of the optic nerve in any of the enucleated eyes, although two eyes did show invasion of the optic nerve head. In neither case did the infiltration extend beyond the lamina cribrosa. In two children there was evidence of choroidal invasion, which was minimal in both cases. Details of the histology of the enucleated eyes are shown in Table 2. The interval from diagnosis of retinoblastoma to development of the ectopic intracranial tumour ranged from 4 to 70 months, median 34 months. The diagnostic investigations and site of the ectopic tumour are listed in Table 3. In all cases the diagnosis was initially made on radiological evidence, confirmed by histology in the four children who underwent surgery. No patient in this series had myelography at the initial diagnosis of intracranial disease. Chromosome studies were carried out on two children, and both were normal, though high resolution banding studies were not done.

Table 2 *Histology of enucleated eyes*

Patient no.	*Differentiation*	*Choroidal invasion*	*Optic nerve invasion*
1	Well differentiated	None	None
2	„	„	„
4	„	„	„
6	„	Yes	Nerve head only
8	„	Yes	None
9	„	None	„
10	Poorly differentiated	„	Nerve head only
11	„	„	None
12	Well differentiated	„	„

Table 3 *Proof of diagnosis of ectopic intracranial retinoblastoma*

Patient no.	*Site of ectopic retinoblastoma*	*Radiology*	*Histology*
1	Pineal region	Ventriculogram	None
2	„ „	„	None
3	Suprasellar region	Carotid angiogram	Yes
4	Pineal region	CT scan	None
5	„ „	„ „	Yes
6	„ „	„ „	Yes
7	Suprasellar region	Carotid angiogram	Yes
8	Pineal region	CT scan	None
9	„ „	„ „	None
10	Suprasellar region	„ „	None
11	„ „	„ „	None
12	Pineal region	„ „	None

Table 4 *Treatment of ectopic intracranial retinoblastoma*

Patient no.	*Treatment of ectopic tumour*	*Response*	*Subsequent outcome*	*Interval from diagnosis of ectopic tumour to death*
1	RT 30 Gy to cranium + cyclo	NE	Spinal metastases at 7/12	13/12
2	RT 54 Gy to cranium + chl	NE	NK	8/12
3	RT 25 Gy to cranium	Partial	Spinal metastases at 8/12	9/12
4	None	—	Progressive disease	1/12
5	Surgical resection RT 46 Gy to midbrain + chemo	Complete	Spinal metastases at 5/12	17/12
6	RT 50 Gy to midbrain + 30 Gy to spine	Complete	Spinal metastases at 6/12	8/12
7	None	—	Progressive disease	4/12
8	RT 20 Gy to midbrain	None	Spinal metastases at 1/12	5/12
9	None	—	Progressive disease	2/12
10	RT 38 Gy to cranium	Complete	Spinal metastases at 2/12	4/12
11	RT 24 Gy to cranium + CVA × 1	Partial	Relapse at primary site at 3/12 + meningeal dissemination at 6/12	9/12
12	None	—	Progressive disease	1/12

RT = external beam irradiation. Cyclo = cyclophosphamide.
Chl = chlorambucil. CVA = cyclo + vincristine + adriamycin. NE = not evaluated. NK = not known.

TREATMENT OF THE ECTOPIC INTRACRANIAL RETINOBLASTOMA

Details of the treatment given to the children and their subsequent outcome are shown in Table 4. Four children received no specific treatment for the ectopic tumour, and all died within four months. Six children received radiation to the midbrain and cranium. Five of these developed spinal metastases within six months. The sixth child (patient 2) died 8 months following radiotherapy but the nature of his relapse is not known. Three of these six children also received chemotherapy. One child received whole neuraxis radiation with 50 Gy to the midbrain and 30 Gy to the spine but developed spinal metastases six months following radiotherapy. In the remaining child surgical resection of the pineal tumour was possible and was followed by radiation (46 Gy) to the midbrain. No spinal radiation was given, and this child developed spinal metastases five months after diagnosis, though there was no clinical or radiological evidence of recurrence at the primary site.

The three children who received between 24 and 25

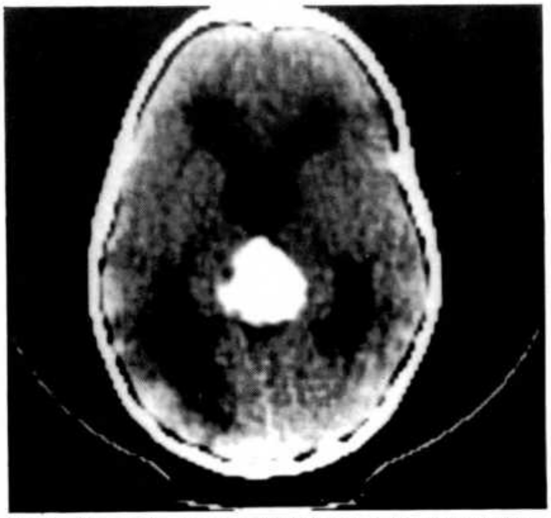

Fig. 1 *CT head scan of patient 8 showing discrete calcified mass in the pineal region with hydrocephalus of the IIIrd and lateral ventricles.*

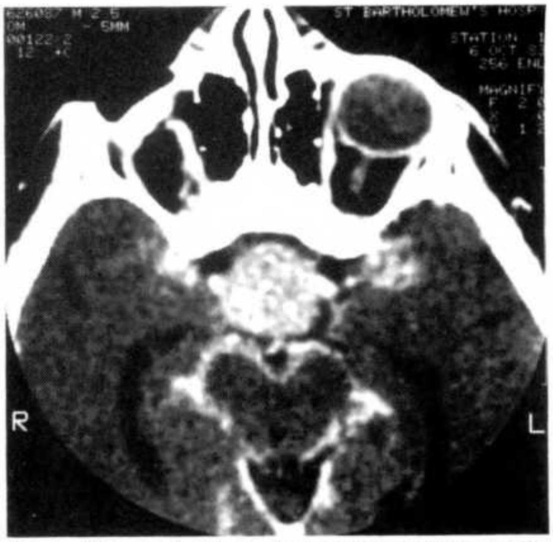

Fig. 2 *CT scan of patient no 11 showing mass in suprasellar region.*

Gy to the pineal region showed only partial resolution of the primary lesion on radiological criteria, whereas one child given 50 Gy to the midbrain had complete resolution of the primary lesion on CT scan with no evidence of recurrence at the primary site at necropsy. Unfortunately spinal irradiation in a dose of 30 Gy did not prevent the development of spinal metastases in this child. The child treated with 54 Gy to the primary lesion went abroad after completion of treatment, and so it was impossible to assess the response of the primary lesion to radiotherapy.

Discussion

Retinoblastoma is an eminently curable cancer of childhood, with an overall 5-year survival rate in excess of 85% in the United Kingdom.[7] It is a highly radiosensitive tumour, and large tumours are effectively treated by external beam radiation conventionally fractionated to 40 Gy. Smaller tumours are treated by photocoagulation or cryotherapy alone. In most cases metastatic disease is initially responsive to vincristine and cyclophosphamide, but the relapse rate is high and there are no published reports of long-term survival.

The child with an ectopic intracranial tumour presents with symptoms and signs of raised intracranial pressure, and on CT scanning a calcified mass is seen in either the pineal or parasellar regions (Figs. 1 and 2). The histology of the ectopic tumour is indistinguishable from a primary retinoblastoma arising in the eye (Figs. 3 and 4). It has been argued that ectopic intracranial retinoblastomas merely represent metastatic spread from the eye. Features which militate against this have been discussed by Bader *et al.*[3] and include the absence of pathological features usually associated with the development of metastases, namely invasion of the optic nerve posterior to the lamina cribrosa, massive choroidal invasion, and intraorbital extension. In addition the discrete nature of the solitary intracranial tumour, in contrast to the typical diffuse leptomeningeal spread or multiple cerebral lesions which usually characterise metastatic retinoblastoma, and also the relatively long latent interval from the diagnosis of retinoblastoma to the development of an ectopic tumour are uncharacteristic of metastatic spread from an embyronic tumour.

Ectopic intracranial tumours occur exclusively in children with bilateral or the genetic form of retinoblastoma. The one child in this series who had unilateral disease (patient 10) is presumed to have had the familial form of retinoblastoma, as her father also had unilateral retinoblastoma. We found a predominance of females developing trilateral retinoblastoma (M:F 1:2) in contrast to the overall excess of males with retinoblastoma (M:F 1.4:1) in the whole series.

In our experience ectopic intracranial retinoblastoma is not common, though in patients with

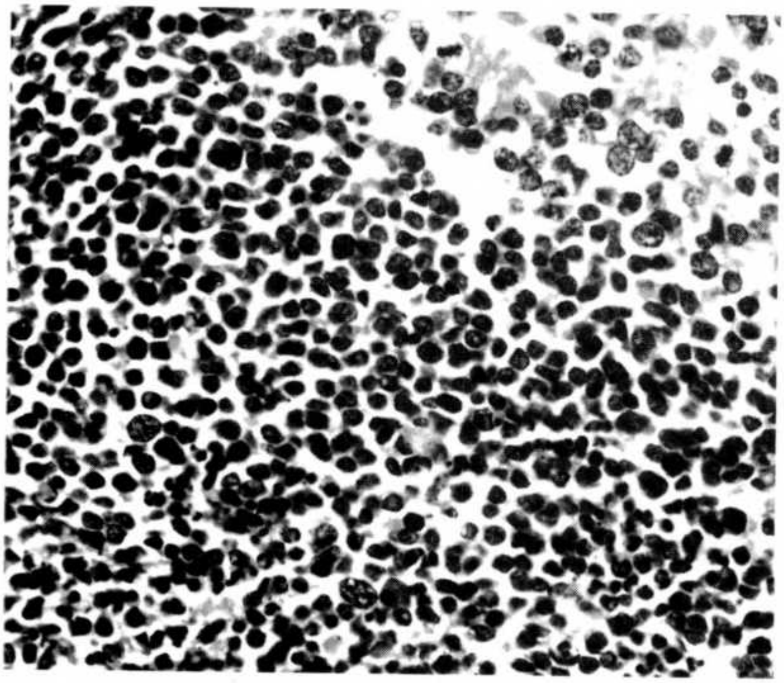

Fig. 3 *Histology of a poorly differentiated ectopic retinoblastoma from patient 3. (Haematoxylin and eosin, ×470).*

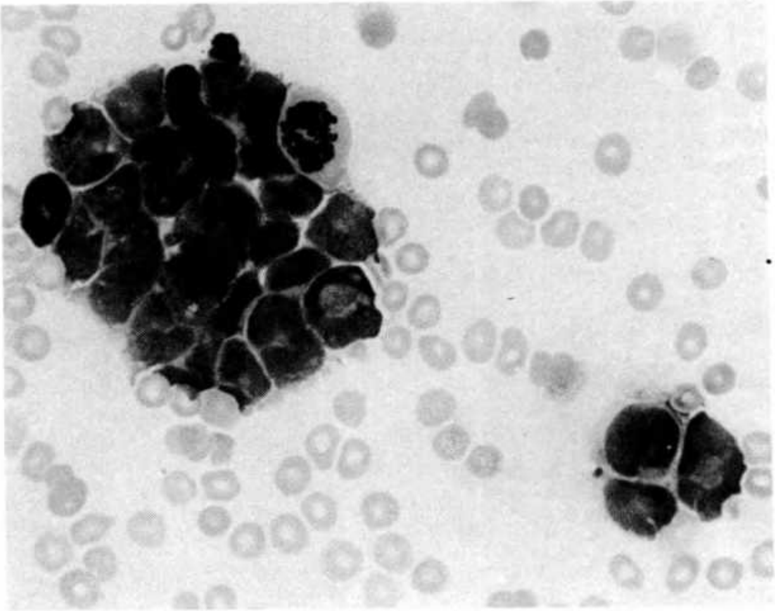

Fig. 4 *Cytospin preparation of CSF from patient 6 at time of relapse, showing clumps of retinoblastoma cells. (Haematoxylin and eosin, ×600, oil immersion).*

bilateral disease it is the most frequent cause of death during the first decade following diagnosis. Among 432 children with bilateral retinoblastoma the prevalence of 'trilateral retinoblastoma' was 2·3%. However, we believe that a more realistic estimate of the prevalence, calculated from the number of cases diagnosed since CT scanning has been available, is about 4%. It has recently been suggested the CT scanning should be part of the routine assessment of all patients with bilateral retinoblastoma,[6] but we consider that the prevalence of the problem is probably too low to justify serial CT scanning of all such patients. However, we accept that a prospective trial is indicated in an attempt to define the role of serial CT scanning in children with bilateral retinoblastoma.

Children who develop ectopic intracranial retinoblastoma appear to have a particularly poor prognosis. This may be due to inadequate treatment of the primary lesion and also to a failure to appreciate the potential of these tumours to metastasise within the central nervous system. From this retrospective review it is apparent that doses of radiation less than 30 Gy are insufficient to eradicate the primary tumour. It is also clear that the major cause of death in these children is the development of spinal metastases.

Consideration of the behaviour and optimal therapy of primary pineal tumours is pertinent to this problem. Primary pineal tumours are highly radiosensitive and radiocurable, with a 66–80% survival in large series.[8 9] Our own experience at St Bartholomew's Hospital agrees with this. It is well recognised that there are different categories of primary pineal tumours and that the pineal parenchymal tumours most relevant to the present discussion, pineocytomas and pineoblastomas, constitute only 12–15% of the total.[4] Recent reports emphasise the propensity of pineal germinomas and pineblastomas to seed via cerebrospinal fluid (CSF) pathways and therefore the necessity for and efficacy of neuraxis radiotherapy.[8]

Specific reports of patients with pineoblastoma and the results of therapy are sparse, but all are informative. In an analysis by the Children's Cancer Study Group of 57 children with biopsy proved pineal and suprasellar tumours there were seven with pineal parenchymal tumours. Of these seven patients six died of their disease, two with spinal metastases, neither of whom had received neuraxis radiotherapy. The dose of radiation to the primary tumour was 50 Gy conventionally fractionated, and the authors imply that local control of the primary was not a signficant problem.[8] Of eight patients (five adults and three children) with pineoblastoma reported on by Borit *et al.*[10] seven died with recurrent tumour within two years of diagnosis and one after an interval of seven years. Leptomeningeal spread, usually extensive, was present in five, but no metastases were encountered outside the central nervous system (CNS). These authors do not state whether the patients received neuraxis radiotherapy. Rubinstein[11] reported a clinico-pathological study of 28 patients with pineal parenchymal tumours of whom 11 had pineoblastomas. Widespread metastases within cerebrospinal pathways were present in all these 11 patients. The author concluded that the entire neuraxis should receive radiotherapy. In contrast to these dismal results of therapy Sung *et al.*[8] reported on two of three patients with pineoblastoma alive and free of disease at three and six years after neuraxis radiotherapy with a total dose of 50 Gy to the primary.

The literature cited suggests that these tumours are radiosensitive, have a propensity to disseminate within CSF pathways, and that with adequate therapy limited to the primary site metastases develop in other CNS sites and are usually fatal within two years.

These conclusions initiate two other discussion points: a child with retinoblastoma who subsequently develops ectopic intracranial disease may have already been treated with radiation. Following a lateral orbital radiation portal the cerebral contribution will be low, but following an anterior megavoltage photon portal to the eye a portion of the underlying brain, including the region of the IIIrd ventricle, will have already received a radiation dose to partial tolerance. Where possible, therefore, we recommend that radiotherapy for familial retinoblastoma should be delivered through a lateral portal.

With regard to relapse at other sites within the CNS, particularly the spine, the analogy with medulloblastoma may be appropriate. Deutsch and Reigel[12] described unsuspected spinal deposits in seven of 16 newly diagnosed children with medulloblastoma, and this high incidence has persuaded many workers, including ourselves, to include myelography in the assessment of patients with medulloblastoma. In cases with positive myelograms the abnormal area is boosted with radiotherapy to a higher dose than the routine 'prophylactic' dose administered to the whole neuraxis. This widely accepted treatment of medulloblastoma may well provide an object lesson for the management of children with ectopic intracranial retinoblastoma.

From our experience it is evident that a more aggressive approach is required for the treatment of children with ectopic intracranial retinoblastoma. We would suggest that combined modes of treatment are most likely to produce a prolonged remission and possible cure. We therefore recommend surgical excision of the ectopic tumour whenever possible, followed by whole neuraxis irradiation 30 Gy, boosting the primary lesion to 50 Gy, or 45 Gy in the very young child. Intrathecal therapy with methotrexate should also be considered.

Reintoblastoma cells have a similar morphology and some surface antigens indistinguishable from those of other neuroectodermal tumours such as neuroblastoma and medulloblastoma. Children with disseminated neuroblastoma respond to intensive combination chemotherapy with vincristine, cyclophosphamide, cis-platinum, and etoposide, and we have observed a partial response to this drug combination in a girl with a primary cerebral neuroblastoma, implying 'access' of these drugs to the CNS. We have recently used this combination of drugs with some success in children with metastatic retinoblastoma. An argument could therefore be made for the administration of intensive systemic chemotherapy in addition to spinal irradiation and intrathecal drug therapy in an attempt to prevent the development of spinal metastases.

In conclusion, ectopic intracranial retinoblastoma is an uncommon condition. In this retrospective analysis of 630 children seen in the ocular oncology units at St Bartholomew's and Moorfields Eye Hospitals over the past 30 years we have identified 12 children with clinical and radiological evidence of this syndrome. It is possible that the condition has been underdiagnosed and that some children thought to have died from intracranial metastases may initially have had localised ectopic pineal tumours. Undoubtedly the advent of CT scanning during the past decade has facilitated diagnosis, and indeed eight of our 12 cases have been diagnosed since 1970. We would suggest that the diagnosis of ectopic intracranial retinoblastoma should be considered in all children with retinoblastoma who develop symptoms or signs of raised intracranial pressure or evidence of cerebral metastases.

A greater experience and understanding of the management of children with ectopic intracranial retinoblastoma is needed to improve the current dismal prognosis, and in view of the rarity of the condition we would suggest that such children should be referred to a centre with a special interest in the condition.

We thank Professor L E Zimmerman for his helpful comments and encouragement, Miss Chrysanthopolou at the Institute of Ophthalmology and members of the Childhood Cancer Research Group in Oxford for their assistance in the ascertainment of cases, and the numerous clinicians who provided follow-up information. We are grateful to Dr A G Stansfeld and Dr O M Curling for providing the photographs reproduced in Figs. 3 and 4 respectively

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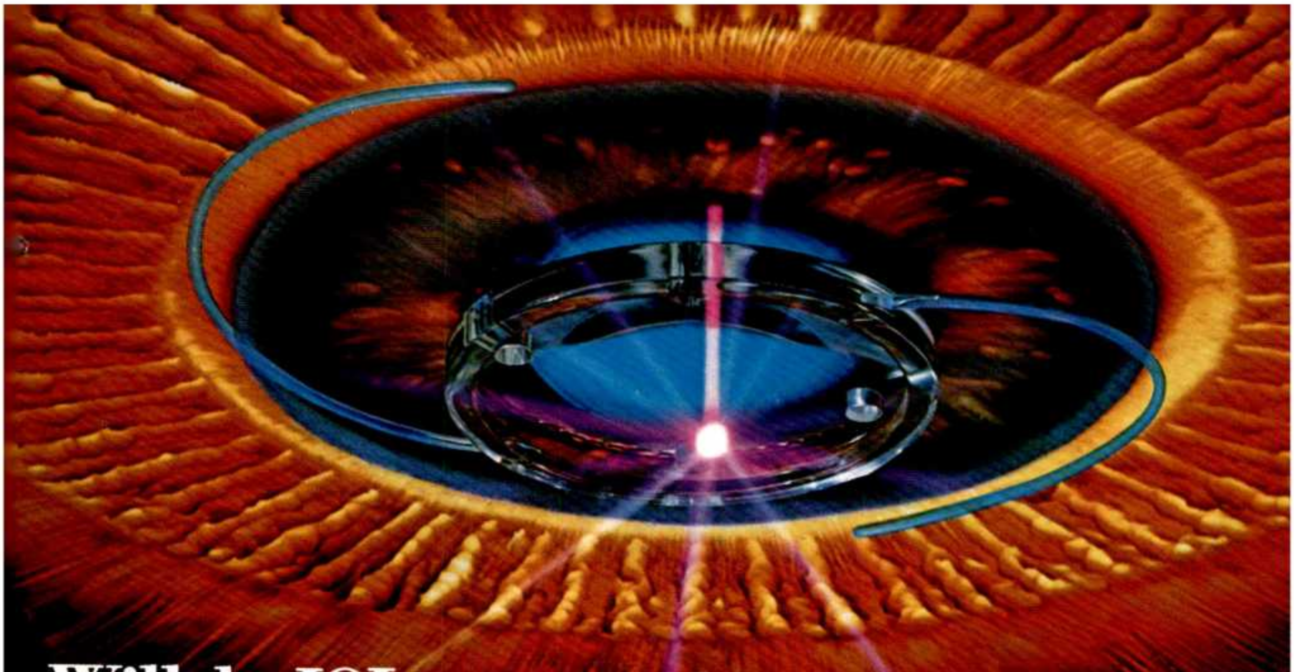

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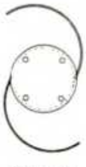

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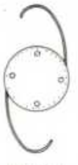

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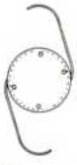

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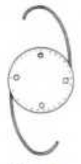

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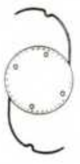

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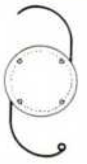

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Pineal malignant neoplasm in association with hereditary retinoblastoma

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SUMMARY A patient with unilateral hereditary retinoblastoma who was successfully treated at the age of 7 weeks developed a tumour in the pineal region two and a half years later. The initial response to radiation treatment of the latter lesion was not maintained. Subsequent necropsy findings are described. Clinically and pathologically this case represents an example of the recently described trilateral retinoblastoma. The response to treatment after early recognition was disappointing.

Several reports have described the occurrence of second malignancies in patients treated for bilateral retinoblastoma.[1-12] One report[3] included three patients with intracranial malignancies, of which one was clinically a pinealoma. In 1977, Jakobiec *et al.*[13] described two neuroblastic intracranial tumours in patients with retinoblastoma, one of which was a pineal tumour. More recently the association of a pineal tumour with bilateral retinoblastoma has been described and the concept of trilateral retinoblastoma suggested.[14-18]

The following case report illustrates the occurrence of a pineal neoplasm in a patient with hereditary unilateral retinoblastoma.

Case report

The patient was a boy whose mother and sister had both been treated for bilateral retinoblastoma. The pregnancy and delivery were normal. The eyes were examined under anaesthetic (EUA) at the age of 7 weeks because of the strong family history of retinoblastoma. A white fluffy lesion measuring 10·5×9 mm was seen in the posterior pole of the left eye. It was situated over the macula and was close to but did not encroach on the optic disc. There were no other lesions of the left eye and there were no tumours in the right eye. There were no other physical abnormalities. A diagnosis of retinoblastoma was made.

The patient was treated with dibromodulcitol 3·5 mg/kg body weight and procarbazine 75 mg/m^2; both drugs were given daily for 33 days. EUA after 11 days showed that the tumour had regressed from the optic disc. After a further 10 days radiation treatment was started with 250kV *x*-rays, 3·5 mm copper half value layer, and a tumour dose of 3095 cGy given. This treatment was given in 17 fractions over a period of 23 days through planned fields to the posterior pole of the left eye. The time dose fraction factor (TDF) was 60 allowing for a relative biological effect of 1·175 compared with cobalt rays.

Five weeks after completion of radiotherapy EUA showed further regression and calcification of the tumour. It measured 7·5×6 mm, and the medial edge was 3 mm lateral to the optic disc. Chemotherapy was resumed in the same dosages as previously and was given three times a week for a further three months.

Subsequent EUAs revealed that the tumour in the left eye remained static, and no tumour was ever detected in the right eye.

At the age of 2 years and 8 months the child developed headaches, episodes of vomiting, and became irritable and lethargic. On examination there was meningism but no other neurological sign. EUA showed that the fundi were unchanged. Computerised tomographic (CT) scan confirmed the presence of a calcified area in the left posterior fundus lateral to the optic disc (Fig. 1). It also showed a 15×22 mm enhancing lesion in the region of the pineal gland

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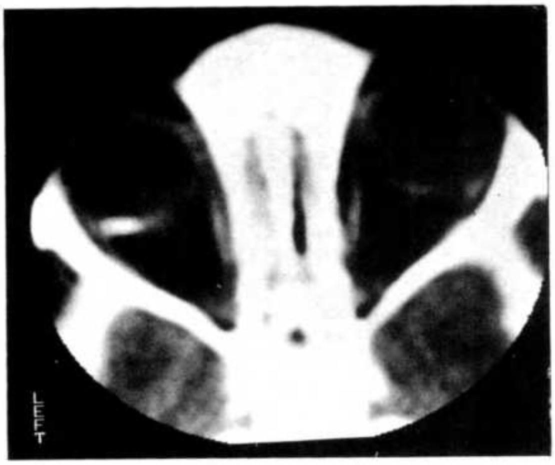

Fig. 1 *CT scan showing calcified tumour in the posterior fundus of the left eye.*

(Fig. 2). There was mild dilatation of the lateral ventricles but no shift of the midline structures. Cytological examination of the cerebrospinal fluid (CSF) showed small malignant cells with pyknotic nuclei (Fig. 3). No tissue was taken for histological examination.

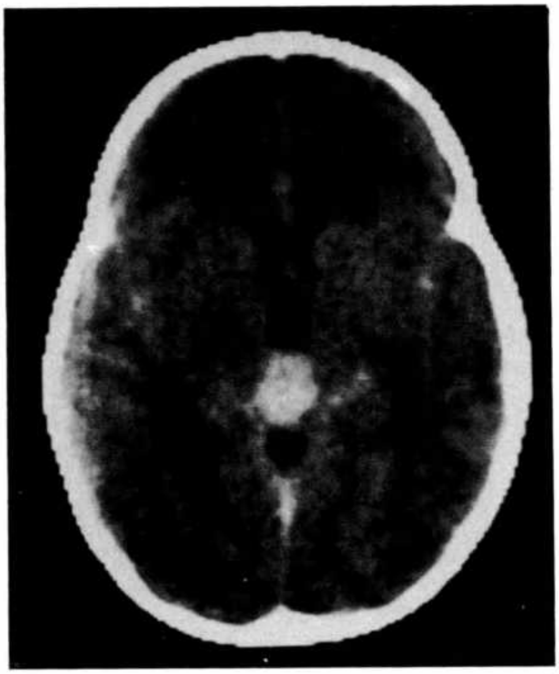

Fig. 2 *CT scan showing an enhancing lesion in the region of the pineal gland and mild ventricular dilatation.*

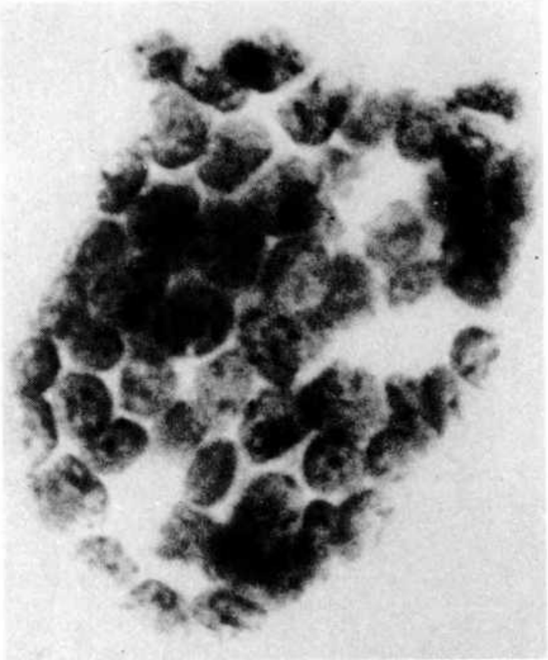

Fig. 3 *Malignant cells in the cerebrospinal fluid showing moulded, small, dark pleomorphic nuclei and rosette formation. (Papanicolaou stain, ×400).*

The patient was treated with dexamethasone 1·5 mg six hourly initially, and this dose was gradually reduced over the following three weeks. The craniospinal axis was irradiated with cobalt-60. The head received 4000 cGy in daily fractions of 120 cGy followed by a further 500 cGy to the pineal area. The spinal cord received 3800–4100 cGy also in daily fractions of 120 cGy. The radiotherapy was protracted over a period of three months because of myelosuppression and intercurrent infections.

A CT scan performed seven weeks after the start of the irradiation showed reduction in the size of the pineal lesion to 10×10 mm and resolution of the hydrocephalus. Cytological examination of the CSF revealed many undifferentiated cells, most of which were degenerate.

The patient remained well for one month after the completion of irradiation, when the headaches, vomiting, and lethargy recurred. A further CT scan showed moderate dilatation of the ventricles, enlargement of the pineal lesion to 24×14 mm, and a second 20×20 mm lesion in the region of the right caudate nucleus. The CSF contained numerous anaplastic tumour cells. Bone marrow biopsy was normal, and there was no evidence of other metastases. The patient was not given any further active treatment and died two months later.

POST-MORTEM FINDINGS

The post-mortem interval was approximately six hours. The body weighed 10·5 kg and showed alopecia. The scalp and skull were otherwise unremarkable. The central nervous system (brain and spinal cord) and the posterior half of each eye together with attached optic nerves were fixed for six weeks in 10% formol saline prior to examination.

The external surface of the brain and spinal cord showed extensive superficial spread of tumour (Fig. 4a). Deposits of tumour were found on the surface of both optic nerves. A large haemorrhagic mass of tumour was present over the cribiform plate. It measured approximately 3 cm in diameter and involved the adjacent cerebral cortex on the inferior aspect of the frontal lobes. The optic chiasm was covered by a thick cake of tumour which extended into the third ventricle. Further deposits of tumour covered many of the cranial nerve roots. The neoplasm gave rise to a malignant meningitis involving much of the inferior aspect of the mid-brain, hind-brain and cerebellar hemispheres. Obstruction of the foramina of Luschka and Magendie was seen.

Similar subarachnoid spread of tumour gave rise to widespread involvement of the spinal cord and peripheral nerve roots. This process extended from the cervical region to the cauda equina. In the cervical and lumbar region, tumour was seen to invade the adjacent spinal cord.

The ventricular system was dilated owing to obstruction of the outlets of the fourth ventricle by tumour. Numerous subependymal deposits of tumour were present in the walls of the third ventricle. The pineal gland was largely destroyed by a mass of tumour measuring approximately 6 cm in diameter which protruded into the third ventricle and extended into the lateral walls of the thalamus and cerebral peduncles (Fig. 4b).

Histological examination of the tumour deposits showed a similar appearance in all lesions sectioned. The features were those of a poorly differentiated neuroectodermal tumour. The cells were poorly preserved. They had small dark basophilic nuclei and scant eosinophilic cytoplasm. Ill defined rosettes of tumour cells were seen. Perivascular growth of malignant cells was noted and much of the tumour was necrotic. Tumour was present within residual pineal tissue and possibly arose from this site.

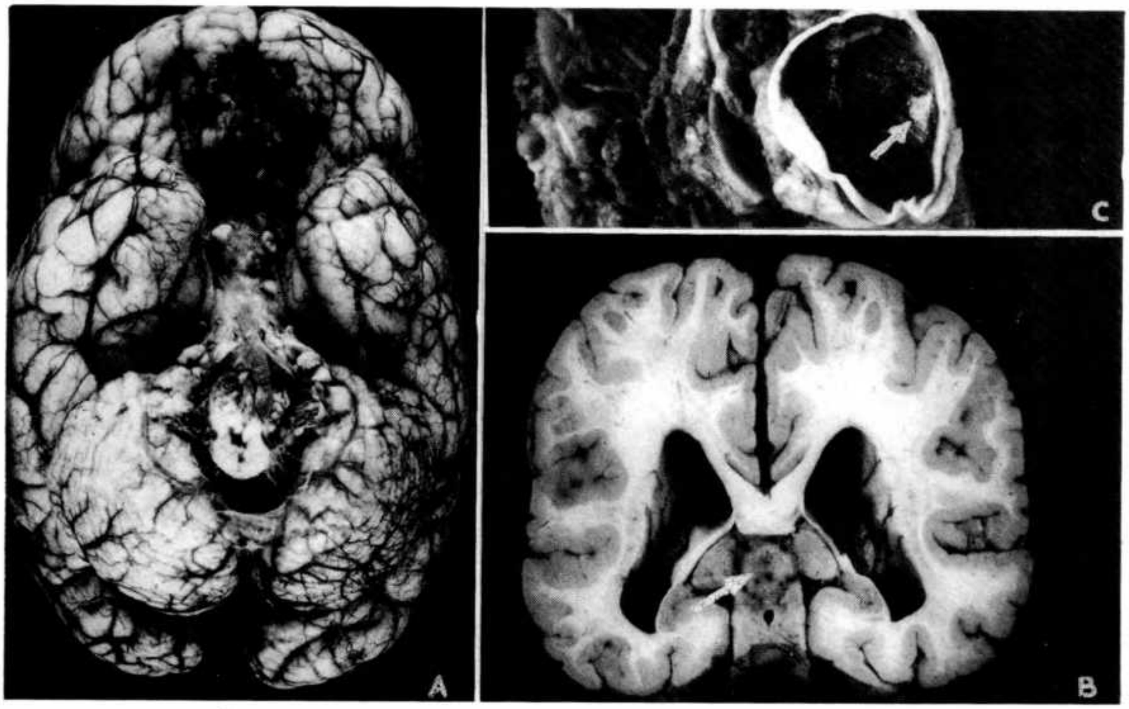

Fig. 4 A: *The inferior surface of the brain showing a large haemorrhagic mass of tumour in the region of the olfactory nerves. Diffuse spread of tumour over the surface of cranial nerves and basal meninges was present.* B: *The coronal section of brain showing large tumour (arrow) in the region of the pineal gland which extended into the cerebral peduncles. Note the dilatation of the ventricular system.* C: *The small calcified retinoblastoma found at necropsy in the left retina (arrow).*

A small focus of involuted calcified retinoblastoma was present in the lateral aspect of the left retina (Fig. 4c), but no residual viable tumour was present in the left eye. Although there was spread of tumour between the dura and the perineureum of the left optic nerve, the neoplasm was not seen to invade the lamina cribrosa. Tumour was not found in the right eye, but similar spread was present along the right optic nerve as far anteriorly as the lamina cribrosa.

Other post-mortem findings included a horseshoe kidney and bronchopneumonia, which was the immediate cause of death.

Discussion

In 1977 'the occurrence of independent brain tumours in two patients with retinoblastoma' was reported.[13] The lesions were both neuroblastic: one was sited in the pineal organ, the other in a retrochiasmal position. Subsequently an association has been reported between bilateral retinoblastoma and secondary primary putative retinoblastomas of the pineal.[14] These workers proposed the concept of trilateral retinoblastoma and suggested that retinoblastoma may arise in vestigial photoreceptors in the pineal. This thesis has been reiterated subsequently.[15 16] The entity is considered to be clinicopathologically distinct from the more common case of retinoblastoma with a second primary sarcoma.[1–12]

In lower vertebrates the pineal organ is photoreceptor,[19] comprises cells very similar to the rods and cones, and is derived from a similar neuroepithelial cell line.[20] The mammalian pineal organ has lost its direct photoreceptor function but retains its sensitivity to photic stimuli through the inferior accessory optic tract mediated via the superior cervical autonomic ganglion.[20] A similar situation is thought to pertain in humans.[21 22] While the occurrence of residual photoreceptor cells in the normal human pineal organ has not been documented,[23–31] pinealoblastomas have been reported to show occasional features usually associated with retinoblastoma.[32] In this context the review[17] emphasising the similar appearance of primitive neuroepithelial tumours arising from different sites is of importance.

The common embryological origin of retinoblasts and pinealoblasts[34] may well account for the susceptibility of both organs to the oncogenic factors operative in individuals carrying the retinoblastoma gene.

The present case may represent an example of this entity. The patient had a strong family history of hereditary retinoblastoma He presented at the age of 7 weeks with a lesion of the left retina which had the appearance of a retinoblastoma and was treated accordingly. Subsequent post-mortem examination showed the presence of a calcified retinoblastoma restricted to the left retina, confirming the clinical diagnosis. Although the patient did not develop a tumour in the right eye, it is certain that he carried the retinoblastoma gene. All 11 patients in Bader and colleagues' series[15] had bilateral tumours, and seven of them had a positive family history. They presented at an average age of 6 months compared with the range of 8–22 months in several series of bilateral retinoblastomas and 24–43 months for unilateral retinoblastomas.[9 14–17]

The sequence of clinical events in the case reported here is suggestive of the development of a second primary lesion rather than a metastatic lesion. The neoplasm of the retina was treated successfully by local radiotherapy, did not recur, and at necropsy was calcified and limited to the retina. Two and a half years later the patient developed symptoms of an intracranial lesion. Although the histological appearance of this second lesion was not known until after death (and a full course of radiotherapy), CT scan localised the neoplasm to the region of the pineal organ. Despite the therapy the child developed numerous intracranial and spinal metastases and died.

At necropsy extensive disease in the central nervous system made assessment difficult. However, tumour was found only in the perineural subarachnoid space and not in the substance of either optic nerve. Viable tumour was not found in either retina nor crossing the lamina cribrosa of either eye. It was considered that the neoplastic cells in the subarachnoid space had metastasised from the intracranial site The capacity of the lesion to spread in the subarachnoid space was evident by the extensive metastases covering spinal nerve roots.

At necropsy the second tumour showed the microscopic features of a poorly differentiated neuroepithelial neoplasm. In accordance with the view of Jakobiec and colleagues[17] and Becker and Hinton[18] only certain knowledge of the site of origin of the lesion could have separated retinoblastoma from pinealoblastoma. The early CT scan suggested that the lesion arose in the pineal organ, and at necropsy tumour was intimately part of residual pineal tissue. These factors favour the opinion that the second lesion was a new and distinct neuroepithelial neoplasm—a component of the so-called trilateral retinoblastoma.

The results of treatment, where it has been instituted, have been unsuccessful.[13 17 18] All patients have died except for two who were said to be alive with disease at one and 10 months respectively.[15] In this case the response to aggressive treatment after early recognition of the entity was disappointing. However, the prolonged overall time of treatment, three months instead of six weeks, could have allowed tumour regrowth between treatments. The use of prior chemotherapy, therefore, with possible myelosuppression, is to be avoided. Alternatively these tumours may have a hypoxic element and be radioresistant.

This tumour had an initial volume of 2·4 cm^3 and thus might be expected to have a cell volume of $2{\cdot}4\times10^9$. A dose for 37% cell survival of 130 cGy might therefore be expected to allow tumour eradication with a dose of 2860 cGy if all cells were to be oxygenated. The failure of a dose 1·5 times larger than this would suggest the presence of hypoxic cells and thus strategies for improved therapy.

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Pigment epithelial pattern dystrophy: a peripheral type

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SUMMARY A hitherto undescribed form of pattern dystrophy of the retinal pigment epithelium was found in a patient suffering from mucopolysaccharidosis II or Hunter's disease. We propose the name peripheral pattern dystrophy.

The pattern dystrophies of the retina are characterised by pigmented, non-elevated changes in the retinal pigment epithelium (RPE) that block background fluorescence at all stages of the fluorescein angiogram. As a rule they are inherited in an autosomal dominant way. A slightly reduced visual acuity has sometimes been mentioned, but a reduced electro-oculogram (EOG) is one of the only consistent findings. Among the pattern dystrophies are reticular dystrophy, fundus pulverulentus, butterfly dystrophy, macroreticular dystrophy, and horseshoe dystrophy.[1] Up till now no relation between a pattern dystrophy and a generalised disorder has been described.

Here we report a hitherto unpublished type of RPE dystrophy in a patient with biochemically proved mucopolysaccharidosis (MPS) II, or Hunter's disease, for which we suggest the name peripheral pattern dystrophy.

Case history

The proband, born in 1965 at term after a normal pregnancy, was the fourth son of non-consanguineous parents (Fig. 1). There were no perinatal problems. His eldest brother had MPS II, but otherwise there were no abnormalities in the family. At the age of 7 it became clear that the proband was also afflicted by MPS II. His mental development was normal. In 1979 an iduronide-2-sulphate-sulphatase deficiency was demonstrated in

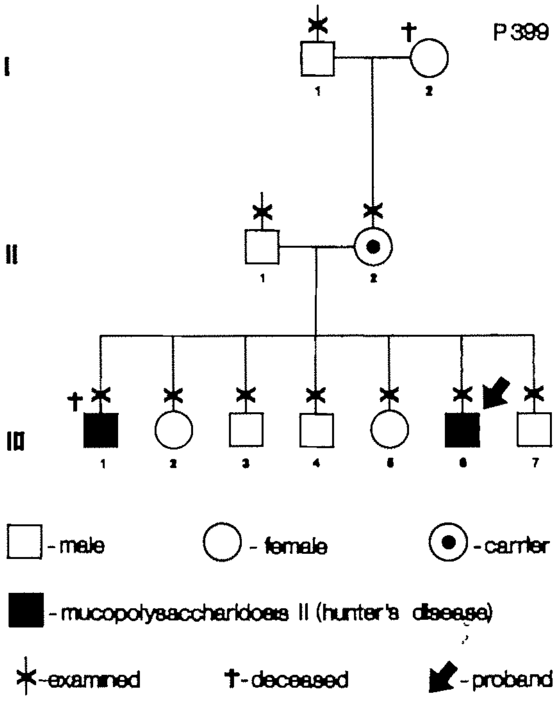

Fig. 1 *Pedigree of the proband's family.*

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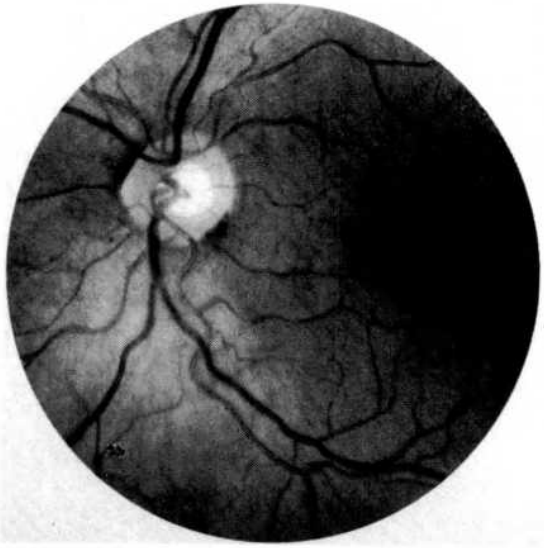

Fig. 2 *Fundus picture of proband's left eye in 1979. Note fine radial folds around the fovea.*

skin fibroblast cultures of the proband and his brother, indicating MPS II.

The first eye examination was performed in 1978. Both eyes had a visual acuity of 6/6 and a refraction of +1·00. There were no corneal opacities. On funduscopy there was a normal macular reflex. At the periphery no abnormalities were found.

In 1979, however, for the first time fine radial retinal folds were noted as well as slightly blurred disc margins (Fig. 2). Thereafter the patient visited the outpatient department every six to eight months. Extensive pigmented lines all around the periphery of the right eye (Figs. 3, 4) became visible for the first time in 1980. These lines, parallel to the limbus, located at the equator, had radial extensions towards the ora serrata. Gradually they became more and more pigmented, and a fine pigment clump appeared exactly in the centre of the fovea. At the end of 1983 vague pigmented lines became visible for the first time in the left eye. In July 1984 V-shaped pigmented lines were present at 9 and 11 o'clock in the periphery of the left eye similar to those at 3 o'clock in the right eye (Figs. 3, 4). On Goldmann perimetry a slightly enlarged blind spot was found. The final threshold of rod dark adaptation was raised by 1·5 to 3 log units (Goldmann-Weekers), while the light rise response was within normal limits. Ganzfeld light flash stimulation revealed normal rod and cone mediated a and b waves in the electroretinogram (ERG) with lowered oscillatory potentials. The ERG, evoked with a 1° and 80% contrast check reversal movement, was also normal, whereas the visually evoked potentials (VEPs) to the same stimulus showed normal amplitudes and slightly prolonged latencies in the right eye and clearly lowered and delayed responses in the left eye. Most of the methods used have been described.[2] Examination of the living family member of the proband (Fig. 1) showed no pigment epithelial changes.

The elder brother of the proband with MPS II died of tracheomalacia. His eyes were slightly autolytic at histological examination. No pigment epithelial abnormalities could be found, however.

Discussion

In some cases of MPS II pigment epithelial changes have been described, but nearly always resembling a tapetoretinal dystrophy.[3-7] In most reports on MPS, however, there has been no mention of any biochemical means of detecting the enzyme defect. Thus it is possible that different types of MPS have been wrongly classified under one heading. On the other hand many patients have been described with no pigmentary abnormalities. We have personally examined four more patients with biochemically proved MPS II but without pigment epithelial abnormalities. We classify the linear, non-elevated, pigmented lines of the proband that blocked fluorescence during the angiogram as a new type of pattern RPE dystrophy. The lines show some resemblance to macroreticular dystrophy, but this dystrophy has so far been described only in the posterior pole.[8,9]

We have seen these lines, much less extensively developed, only in patients with longstanding choroidal or retinal detachments. In the retinal detachment cases the high-tide marks probably represent linear reactive hyperplasia of the pigment epithelium. In our patient no retinal or choroidal detachment or uveal effusion has been seen, though he has had an ophthalmic check-up every six to eight months since 1979. Nor could any sign of vitreous traction bands be found on biomicroscopy. Patients with peripheral drusen often have a reticular pattern dystrophy of the RPE, but our patient had no drusen. The absence of any of these signs in the left eye at the time that the pigmented lines are developing also points to a genuine pigment epithelium dystrophy. The radial retinal folds in the posterior pole show a resemblance to those found in X-linked juvenile retinoschisis, but in our proband no schisis could be found, even though indentation biomicroscopy was performed. His visual acuity was also not consistent with such a diagnosis. We have previously discussed pattern dystrophies more fully.[1]

The eyes of the elder brother, who died because of tracheomalacia, were obtained for histological study.

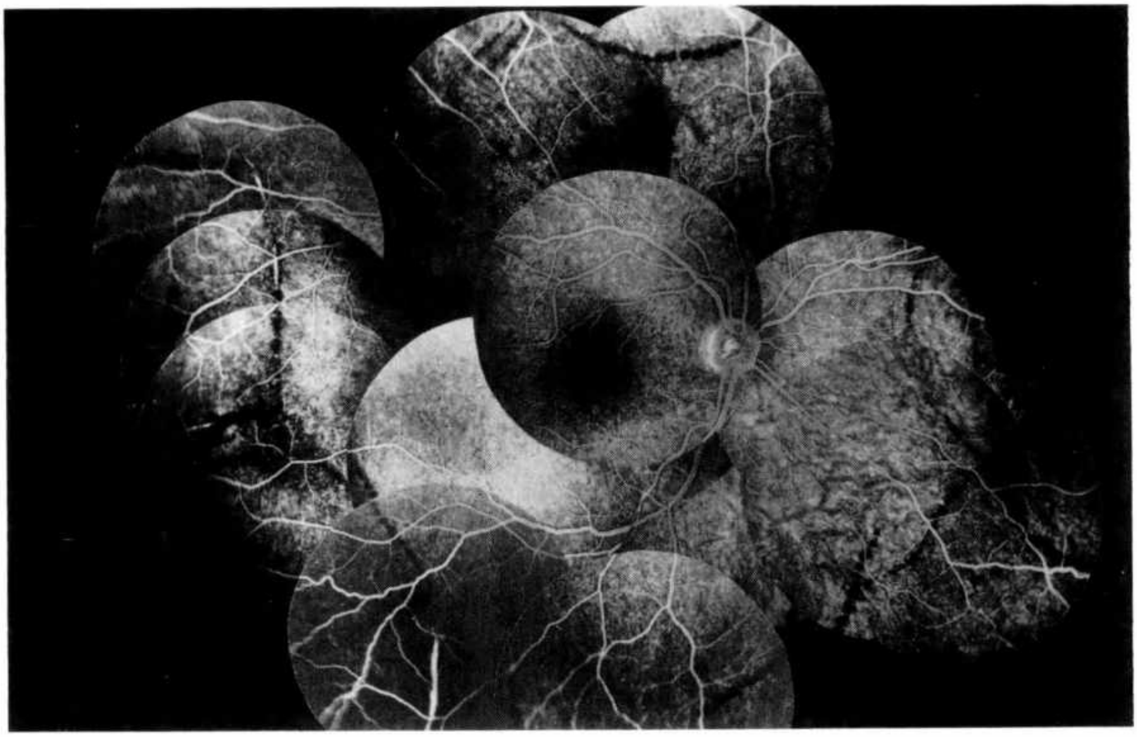

Fig. 3 *Composite fundus picture of the right eye of proband in 1982. Late arteriovenous phase of fluorescein angiogram. Note peripheral pigmented lines. Because of deep set eyes the far periphery could not be photographed.*

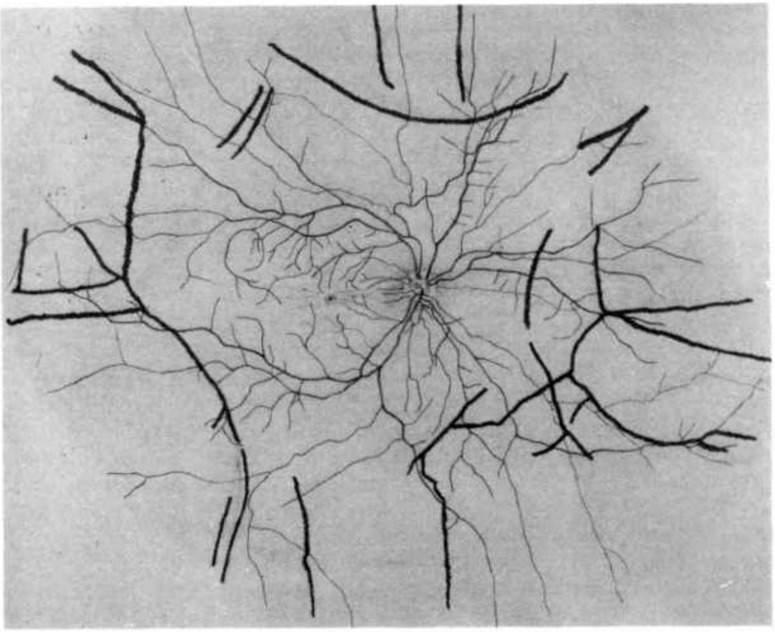

Fig. 4 *Schematic drawing of pigmented lines in the same eye as seen by indirect ophthalmoscopy.*

Although they were slightly autolytic, no pigment abnormalities were seen.

There are findings that do not exactly fit in with the diagnosis of pattern dystrophy of the RPE. Although the standing potential of the EOG was low, there was still a good light rise. Moreover the dark adaptation curve and the delayed latencies on testing the VEP were abnormal. The VEP abnormalities, however, have been mentioned more often in patients with MPS II[10] and probably are due to accumulation of mucopolysaccharides in the optic nerve, resulting in blurred discs.

We have found no reports of pattern dystrophies in patients with MPS II. Moreover the four patients we have examined had no pigmentation in the periphery. It may be possible that in some of these patients, who are sometimes difficult to examine, pigmentations in the fundus periphery have been overlooked. On the other hand we believe that up till now there is insufficient support for the suggestion that the fundus pigmentation in our proband with MPS II is more than a coincidental finding.

We would like to thank C B Schotel and T Put for their art work and Mrs C H M Muijlwijk-Planting and Mrs M A T Booth-Hoppenbrouwers for their secretarial help

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Autoimmunity in hereditary retinal degenerations. II. Clinical studies: antiretinal antibodies and fluorescein angiogram findings

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SUMMARY Testing by indirect immunofluorescence for the detection of antiretinal antibodies and lymphocyte stimulation for cell-mediated immunity to retinal antigens was performed on blood obtained from 59 patients with retinitis pigmentosa (RP) and 29 without RP who had other types of retinal disease. The results from the patients' immunological studies were correlated in a masked fashion with six parameters of the fluorescein angiogram: disc staining, peripapillary oedema, vascular arcade oedema, macular oedema, and focal vascular staining (late phases), and disc telangiectasia (early phases). Significant correlations for both groups together were found for IgG antiretinal antibody reactivity and macular oedema ($p<0{\cdot}038$) and disc staining ($p<0{\cdot}033$). The non-RP retinal disease group had more significant correlations, including IgG antiretinal antibody reactivity with vascular arcade oedema ($p<0{\cdot}018$), disc staining ($p<0{\cdot}018$), and peripapillary oedema ($p<0{\cdot}023$); the RP patients had significant correlation with IgG reactivity and arcade oedema ($p<0{\cdot}045$). With combinations of IgG, IgM, and lymphocyte reactivity various significant correlations were found with the fluorescein angiogram.

Numerous laboratory studies support the notion that a variety of acquired and hereditary retinal diseases have autoimmune components, and reports to date have emphasised the presence of cell-mediated immunity or antiretinal antibodies to various retinal antigens in these patients. Whether a pathological role is played by these antibodies or by lymphocytes showing sensitisation to retinal antigens has been more difficult to determine. Retinal tissue is rarely available for direct study, and indirect methods are usually employed to investigate the possibility of immunopathogenicity in the retinal degenerations.

Clinicopathological correlations have been attempted by several investigators. Dumonde *et al.* examined sera from patients with various forms of retinal vasculitis for the presence of complement and antiretinal antibodies.[1] In addition to identifying immunological activity they also attempted to correlate its degree with the severity of the systemic and retinal vasculitis. In patients with only ocular involvement retinal autoantibodies were found significantly more often those with severe retinal vasculitis than in those who had only mild to moderate disease.

Keltner *et al.* reported on a cancer patient with an unusual retinal degeneration whose serum antibodies were reactive with normal donor retinal tissue by the immunofluorescent complement fixation test.[2]

Numerous studies have established that patients with retinitis pigmentosa (RP) and other retinal degenerations frequently have an immunological response to retinal antigens. Alterations in cell-mediated as well as humoral immunity have been described. Brinkman *et al.*[3] and Heredia *et al.*[4] described retinal antigen stimulation of lymphocytes from RP patients, and Char *et al.* found that lymphocytes from RP patients were significantly more cytotoxic in an assay against a retinoblastoma tissue culture cell line.[5] Increased cellular immune responsiveness to the retinal S antigen has been found in RP patients[6] as well as patients with retinal inflammatory diseases such as birdshot retinochoroidopathy[7] and uveitis.[8]

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Hooks *et al.* recently reported subnormal levels of a lymphokine, interferon-gamma, a product of T lymphocytes from 12 patients with RP. No abnormality of humoral immunity or any increased incidence of infections was detected in these patients.[9]

While Rahi reported increased serum IgM levels in RP patients,[10] a similar study by Spiro *et al.* found no difference in serum IgM levels between RP patients and controls.[11] Kumar *et al.* found antiretinal antibodies by the tanned red cell haemagglutination technique in 60% (15/25) of RP cases that they investigated.[12] Spalton *et al.* using immunofluorescence techniques demonstrated the binding of sera from RP patients to rat photoreceptor cells.[13] Recently our group reported that 37% (43/116) of RP patients and 33% (21/64) of non-RP patients with other retinal disease had antiretinal antibodies by indirect immunofluorescent techniques compared with 2% (1/42) of controls.[14] The same study showed that 19% (16/86) of RP patients and 18% (11/64) of non-RP patients with other retinal eye disease had sensitisation of lymphocytes to retinal antigens when tested with in-vitro transformation assays.[11]

While all these studies strongly suggest that the immune system may have an active role in RP and other retinal degenerations, no study to date has demonstrated a clinical correlation between the presence of immunological response and an objective measure of the patient's disease state.

To ascertain whether antiretinal antibodies and sensitised lymphocytes may have a pathophysiological role in RP and other retinal degenerations, we correlated in a double-masked fashion the fluorescein angiographic findings with the presence or absence of antiretinal antibodies and cell-mediated immunity to retinal antigens in patients with RP and with non-RP ocular disease.

Patients and methods

Fifty-nine patients with all types of RP and 29 with other types of retinal disease, a subset of a larger group previously reported,[11] were examined to see whether the presence of antiretinal immune activity correlated with findings on the fluorescein angiogram. Indirect immunofluorescence staining for IgG and IgM antiretinal antibodies and lymphocyte in-vitro transformation assays to retinal antigens were performed by methods previously reported.[14] Patients selected for study were all those in whom a fluorescein angiogram was obtained as part of their routine diagnostic investigation within two months of venepuncture for the immunological studies. In most cases the fluorescein angiogram was obtained on the same day as the venepuncture was performed, but a few patients had fluorescein angiograms performed on return visits or a few days after the initial visit if an appointment was not available the same day. Selection was not based on any knowledge of the blood results.

Patients with progressive panretinal degeneration and other ocular disorders were evaluated with a comprehensive medical, ocular, and family history (pedigree analysis), ophthalmic examination, and tests consisting of Goldmann visual fields, electroretinogram, dark adaptation final rod threshold, fundus photography, and fluorescein angiography. Patients with hereditary retinal degenerations were classified as precisely as possible by the above tests and examination. RP was diagnosed when the patient had a panretinal degeneration with progressive visual field loss, and an abnormal or unrecordable electroretinogram with no other inflammatory or toxic history to explain the retinal degeneration.

The patients were placed in the following RP subgroups: rod-cone and cone-rod degeneration subdivided by inheritance, and the specific RP types of choroideraemia, preserved para-arteriolar retinal pigment epithelium RP (PPRPE), pigmented paravenous retinochoroidal atrophy, and Usher syndrome. The classification was based on previously published methods and rationale.[15-18] (Pigmented paravenous retinochoroidal degeneration has never been proved to be a hereditary disease but is probably a pattern of degeneration. Whether it should be classified as a form of retinitis pigmentosa is debatable. These patients were included in the RP section because their clinical and functional testing gave similar results to those of many patients with simplex RP. See Heckenlively and Kokame[18].) The designation of cone-rod degeneration was given if there was either electroretinographic evidence that the photopic electroretinogram was worse affected than the rod-isolated electroretinogram or that the final rod threshold was elevated less than 2·0 log units anywhere outside the macular area Rod-cone degeneration was diagnosed if a patient's scotopic electroretinogram was more abnormal than the photopic waveform or if the final rod threshold was elevated, typically 3·4 log units or more. In advanced cases of RP in which the visual field is less than 8° it may not be possible to state whether a patient has the rod-cone or cone-rod pattern of degeneration on the basis of the dark adaptation test alone.

The study was performed in a masked fashion such that the investigators evaluating the fluorescein angiograms had no knowledge of the immunological activity results and vice versa. Detailed methodology for our evaluation of antiretinal antibodies and lymphocyte sensitisation to retinal antigens has been previously published[11] and will be described briefly. Sera from patients with RP and other types of ocular

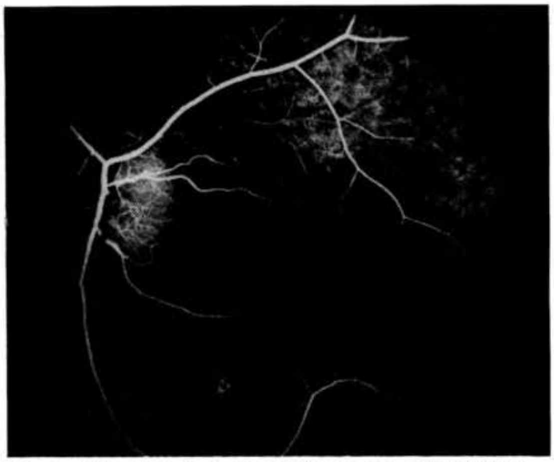

Fig. 1 *Disc telangiectasia, mainly of temporal portion of disc, in 12-year-old boy with progressive cone-rod degeneration. Telangiectasia is most easily seen in early phases of the fluorescein angiogram.*

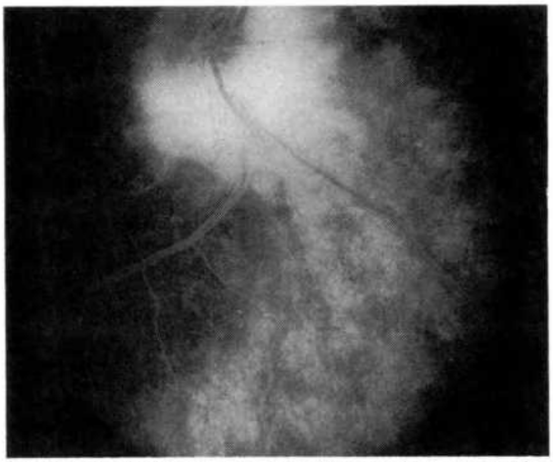

Fig. 3 *Peripapillary oedema in a 20-year-old woman with Usher's syndrome. Hyperfluorescence in the peripapillary region obscures disc margin detail as well as most of the peripapillary retinal vessels. Diffuse retinal oedema is also present.*

disease were placed on normal human donor retinal sections, which were then washed and stained with fluorescein-conjugated goat antihuman IgG and IgM reagents. The sections were examined under a fluorescein microscope and graded for presence or absence of staining. Positive staining indicated the presence of IgG and/or IgM antigens in the patient's serum that bound antigens present on the sections. Peripheral blood lymphocytes obtained as previously described[11] were incubated with T and B lymphocyte mitogens or retinal antigens. Tritiated thymidine was added four hours before harvesting. Sensitisation was expressed as a stimulation index, consisting of a ratio of counts per minute in the presence of antigen divided by counts per minute in the absence of antigen. A stimulation index $>2\cdot0$ was considered an indication of cell-mediated activity against retinal antigen. Lymphocytes obtained from normal volunteers were used for controls for each method.

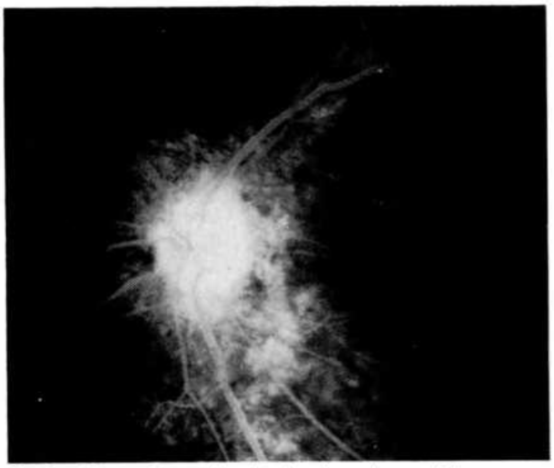

Fig. 2 *Disc oedema, identified on late phases of the fluorescein angiogram, is seen in this patient with severe pigmented paravenous retinochoroidal atrophy (not shown). Leakage of fluorescein causes the disc to be hyperfluorescent, obscuring disc detail, and may even leak into the overlying vitreous space.*

Six angiographic parameters were examined by two investigators: disc telangiectasia, disc staining, peripapillary oedema, arcade oedema, macular oedema, and focal vascular staining. The fluorescein angiographic parameters were scored (1) not present, (2) moderately present, and (3) markedly present. For statistical analysis the latter two groups were combined.

Disc telangiectasia, or dilatation of normal disc surface vessels, has been noted by us in a number of retinal dystrophies, in particular the cone-rod degenerations.[19] These vessels can be identified by abnormal beading of the vessel walls and by the increased numbers of small vessels seen in the early phases of the fluorescein angiogram (Fig. 1).

Disc staining was evaluated on the late phases of the fluorescein angiogram; a positive finding was a brightly hyperfluorescent disc, often with overlying vitreal haze where fluorescein had escaped into the adjacent vitreous (Fig. 2).

Peripapillary oedema, evaluated on the late phases of the fluorescein angiogram, consisted or markedly hyperfluorescent areas covering at least five clock

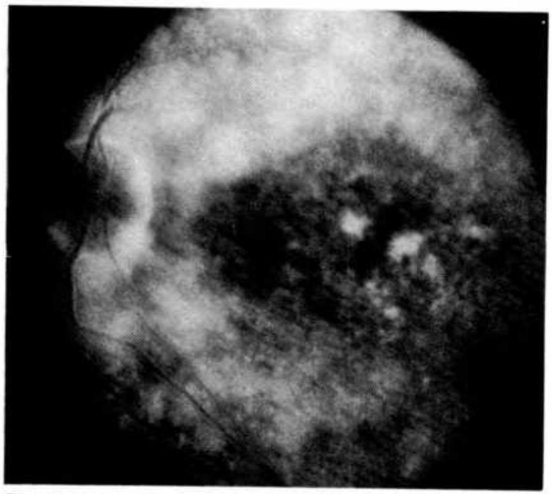

Fig. 4 *Arcade oedema superiorly is particularly marked, though the retinal arcade inferiorly also shows hyperfluorescence. Some macular and peripapillary oedema is also present. Patient is a 35-year-old woman with advanced simplex retinitis pigmentosa.*

hours in the retina adjacent to the disc margin (Fig. 3).

Arcade oedema, evaluated on the late phases of the fluorescein angiogram, was identified when hyperfluorescent areas were noted deep to and adjacent to the vascular arcades of the posterior pole (Fig. 4). No attempt was made to distinguish whether the leakage was derived from retinal vasculature or retinal pigment epithelium.

Macular oedema was evaluated on late phases of the fluorescein angiogram and consisted of either the traditional changes of cystoid macular oedema or diffuse hyperfluorescence of the posterior pole in the anatomical macular area (Fig. 5).

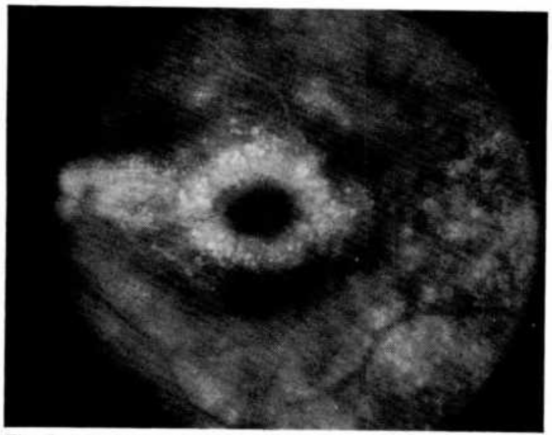

Fig. 5 *Cystoid macular oedema, more in the paramacular region, is noted in this 43-year-woman with advanced simplex retinitis pigmentosa. Diffuse retinal oedema in the superior arcade and marked oedema of the maculopapillary bundle can be seen.*

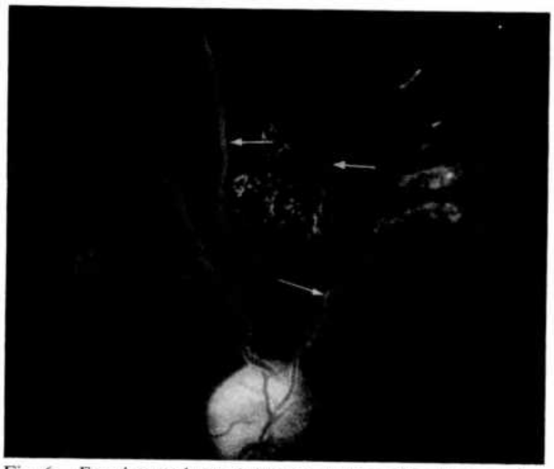

Fig. 6 *Focal vascular staining consisting of focal areas of hyperfluorescence is seen in peripapillary retinal vessels as well as retinal veins and arteries superiorly (arrows) in a 23-year-old man with choroideraemia.*

Vascular staining was noted on late phases of the fluorescein angiogram as focal, often pinpoint, areas of hyperfluorescence which could be seen in venous and arteriolar vessel walls (Fig. 6). Vascular staining was most easily seen in arcade and peripapillary area vessels (Fig. 7). At least two distinct focal areas of hyperfluorescence in a vessel wall were needed to call this parameter moderately present.

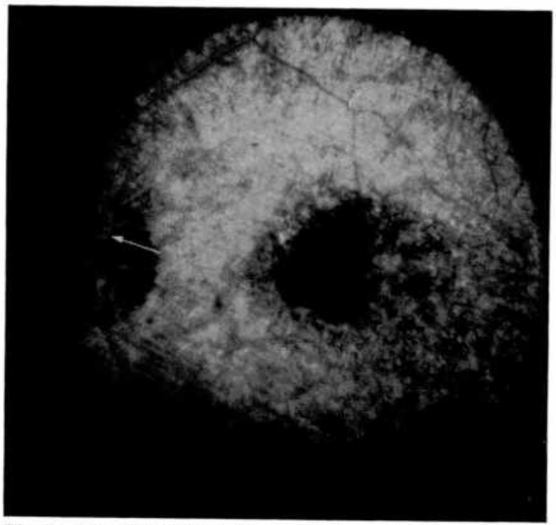

Fig. 7 *Focal vascular staining in peripapillary retinal arteries (arrow), left eye, in a 42-year-old woman with advanced simplex retinitis pigmentosa. Severe diffuse retinal oedema is also present.*

An evaluation of the statistical association between fluorescein findings and immunological indices was performed by the one-tail Fisher's exact test. Group comparisons, such as RP with non-RP and rod-cone with cone-rod degeneration, were made by the Mantel-Haenszel test for homogeneity of χ^2.

Results

Numerous significant correlations were found for all patients and for non-RP patients as a group. The non-RP disease group showed more significant correlations than the patients with RP.

For all patients (Table 1) positive immunofluorescence for IgG antiretinal antibodies correlated significantly with macular oedema ($p<0{\cdot}038$) and disc staining ($p<0{\cdot}033$). A less significant correlation was noted between focal vascular staining ($p<0{\cdot}068$) and presence of IgG, and between the lymphocyte stimulation test and macular oedema ($p<0{\cdot}079$).

In an attempt to locate a cumulative effect, combinations of immunoglobulin activity and/or lymphocycte stimulation were tested for significance; IgG or IgM antibody staining correlated with disc staining ($p<0{\cdot}05$). Combinations of positive IgG and IgM staining, and lymphocyte stimulation tests, resulted in some correlation with focal vascular staining ($p<0{\cdot}07$)

Table 1 *Correlation of immune reactivity with fluorescein angiographic parameters for all patients (RP and non-RP)*

Index of immune reactivity	*Angiographic change*	*Significance (p value). Fisher's exact test*
IgG antiretinal antibody	Macular oedema	<0·038
IgG antiretinal antibody	Disc staining	<0·033
IgG antiretinal antibody	Focal vascular staining	<0·068
Lymphocyte stimulation (to retinal antigens)	Macular oedema	<0·079
IgG or IgM antiretinal antibodies	Disc staining	<0·053
IgG, IgM antiretinal antibodies and lymphocyte stimulation	Focal vascular staining	<0·070

A number of significant correlations were found in the non-RP disease group (Table 2). IgG antiretinal antibody correlated with arcade oedema ($p<0{\cdot}018$), with disc staining ($p<0{\cdot}018$), and with peripapillary oedema ($p<0{\cdot}023$). IgM staining correlated with peripapillary oedema ($p<0{\cdot}011$). For a cumulative effect both IgG and IgM correlated with arcade oedema ($p<0{\cdot}023$), disc staining ($p<0{\cdot}029$), and peripapillary oedema ($p<0{\cdot}003$). Positive IgG, IgM, and lymphocyte stimulation tests together did not correlate significantly with any angiographic parameter. Attempts to subdivide the non-RP group between inflammatory and degenerative causes did not give significant results.

RP patients as a group had fewer correlations. IgG immonofluorescence correlated with arcade oedema ($p<0{\cdot}045$), as did the combination fo IgG and IgM antibodies and positive lymphocyte stimulation ($p<0{\cdot}045$).

When the RP and non-RP groups were compared with each other, numerous significant differences appeared in correlations with arcade oedema and papillary oedema (Table 2).

RP patients were further compared by type of degeneration, that is, rod-cone and cone-rod, and were evaluated by analysis of variance with the non-RP patients (Table 3). The findings from the rod-cone degeneration patients were significant or nearly so in correlations with arcade oedema. The findings from the cone-rod degeneration patients correlated nearly significantly in test correlations with focal vascular staining. No correlation was found between specific RP type and autoimmune reactivity.

Table 2 *Correlation of immune reactivity with fluorescein angiographic parameters by groups (RP and non-RP)*

*Index of immune reactivity**	*Angiographic change*	*Level of significance (p value)*		
		RP	*Non-RP*	*Group difference*
IgG	Arcade oedema	0·045	0·018	0·005
IgG	Disc staining	NS	0·018	NS
IgG	Peripapillary oedema	NS	0·023	0·042
IgM	Peripapillary oedema	NS	0·011	0·057
IgG or IgM	Arcade oedema	NS	0·023	0·011
IgG or IgM	Disc staining	NS	0·029	NS
IgG or IgM	Peripapillary oedema	NS	0·003	0·008
IgG, IgM, Lymph. stim.	Arcade oedema	0·045	NS	0·043
IgG, IgM, Lymph stim	Disc staining	NS	0·069	NS
IgG, IgM, Lymph stim	Peripapillary oedema	NS	NS	0·055

*IgG/IgM=positive IgG/IgM immunoglobulin indirect immunofluorescence Lymph stim =lymphocyte stimulation by retinal antigens
NS=non-significant

Table 3 *Correlation of immune reactivity with fluorescein angiographic parameters by retinitis pigmentosa degenerative type*

*Index of immune reactivity**	*Angiographic change*	*Level of significance (p value)*	
		Rod-cone	*Cone-rod*
IgG	Focal vascular staining	NS	0·063
Lymph stim	Arcade oedema	0·067	NS
IgG, IgM, lymph stim	Arcade oedema	0·011	NS
IgG, IgM, lymph. stim	Focal vascular staining	NS	0·069

*IgG/IgM=positive IgG/IgM immunoglobulin indirect immunofluorescence. Lymph stim =lymphocyte stimulation by retinal antigens
NS=non-significant

Discussion

While this study was originally designed to investigate the potential pathological role of the immune system in RP patients, the most significant results were found in the non-RP ocular disease reference group, which consisted mainly of other types of retinal disease (Table 4). These non-RP patients showed significant correlations between IgG and the combination of IgG and IgM antiretinal antibodies with arcade oedema, disc staining, and peripapillary oedema. IgM staining correlated significantly with peripapillary oedema.

RP patients as a group showed significant correlations between IgG alone and IgG, IgM antiretinal antibodies and lymphocyte stimulation with arcade oedema; when divided into rod-cone and cone-rod degeneration, neither group showed significant correlations singly with any immune index. Only the rod-cone degeneration group showed a significant correlation between the combination of IgG, IgM antiretinal antibodies and the lymphocyte stimulation test together as a cumulative effect with arcade oedema.

The existence of correlations between fluorescein angiographic changes and indices of immune activity may be an indication that the immune system has a pathophysiological role in a number of retinal diseases. This correlation does not clarify whether the observed changes represent a primary pathological process, a secondary effect in a complicated degenerative process, or possibly some type of epiphenomenon. The observation that RP patients show fewer such correlations than non-RP patients may not reflect a lack of immunological activity but rather that the slow defenerative process inherent in RP does not challenge the immune system in the same fashion as the process of inflammatory disease. Eye tissue compared with total body mass is small to begin with, and products from a retinal degeneration would not be a large antigenic challenge.

Table 4 *Diagnoses of patients with non-RP ocular disease*

Birdshot retinochoroiditis
Cataract with macular degeneration
Cataract with retinal detachment
Detached retina
Diabetic retinopathy
Fundus flavimaculatus
High myopia
Macular degeneration (age related)
Macular oedema (after cataract surgery)
Measles retinopathy
Regional choroidal atrophy
Secondary luetic chorioretinitis
Stickler syndrome
Toxoplasmosis
Uveitis

Fluorescein angiography is commonly used for investigating various types of retinal oedema and less commonly for disc telangiectasia. Focal vascular staining on late phases of the fluorescein angiogram is a finding not commonly associated with hereditary retinal degenerations, or even other retinal diseases except vasculitis. The cause of focal vascular staining is unknown, but it could be related to the presence of immune complexes or other immunological entity producing damage to retinal vessels.

Peripapillary oedema was significantly associated with both presence of antiretinal antibodies and lymphocyte sensitisation. Since the peripapillary area, particularly when a conus is present, tends to be unprotected by the blood-retinal and retinal pigment epithelial barriers, it is not surprising that antiretinal immunological mechanisms might damage this area.

The correlations between the fluorescein angiogram and markers of immune reactivity in this study lead us to assume that they reflect secondary rather than primary disease effects and that the pathological influence of immune factors remains to be determined. Indirect immunofluorescent staining with the use of patient sera on human donor tissue has proved valuable in detecting antiretinal antibodies, and it merits further investigation for its development as a possible clinical tool.

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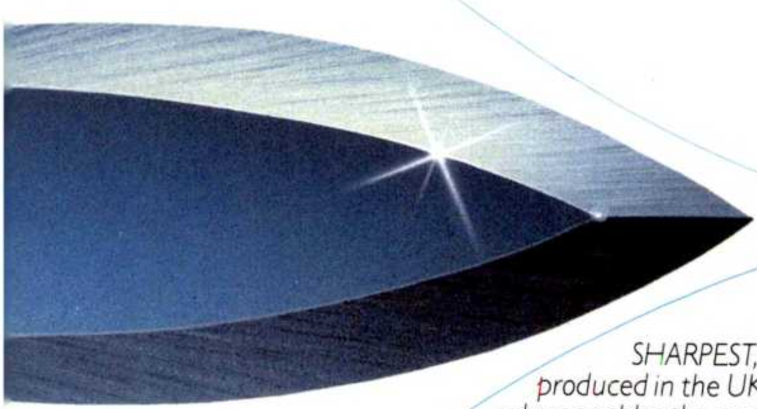

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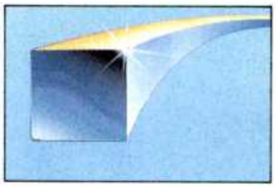

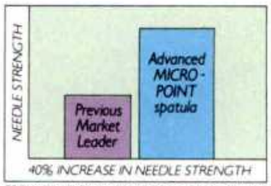

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Blood and plasma viscosity measurements in patients with glaucoma

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SUMMARY Blood viscosity at 10 shear rates, plasma viscosity, packed cell volume, plasma fibrinogen, serum α_2-macroglobulin, and serum proteins were measured in 83 patients with low-tension glaucoma (LTG) and 23 patients with 'high-tension glaucoma' (HTG: at least one IOP reading above 40 mmHg) and compared with those in 50 controls. Blood and plasma viscosity values and packed cell volume were significantly higher in the LTG group than those in controls. The HTG and the LTG groups differed only in plasma viscosity, but smoking and drinking habits in the HTG patients were greatly different from those in LTG patients and controls, thus preventing interpretation of data in the HTG group. Within the LTG group viscosity values were highest in a subgroup designated earlier by us as focal ischaemic LTG, whereas another subgroup, senile sclerotic LTG, did not show significant differences compared with controls. These findings may indicate a factor in the pathogenesis of visual field defects and disc cupping in some patients with LTG.

Low-tension glaucoma (LTG), the combination of typical glaucomatous optic disc and visual field changes, an open anterior chamber angle, and comparatively low intraocular pressure is a well recognised entity. Most theories about the pathogenesis of the visual field defects emphasise the importance of high intraocular pressure (IOP) in primary open-angle glaucoma (POAG) and of vascular disease and related risk factors in LTG.[1]

Risk factors that have been investigated in LTG include large vessel disease,[2] hypertension,[3 4] hypotension and shock,[5 6] diabetes mellitus,[7-9] increased blood lipids,[10 11] abnormal blood coagulation,[10] and blood pressure in the ophthalmic artery.[1] For none of these factors separately could a strong correlation with LTG be established.

The role of increased blood viscosity is suggested in several disease states with impaired perfusion of tissues, such as myocardial infarction,[12 13] angina pectoris,[14] intermittent claudication,[15 16] cerebral infarction,[17 18] the dementia syndrome,[19] and also in the microcirculatory disturbances of diabetes mellitus with proliferative retinopathy[20-22] and retinal vein thrombosis with capillary nonperfusion.[23 24] In a similar way increased blood viscosity might have a role in the pathogenesis of visual field defects and optic disc cupping in LTG patients, whereas in POAG patients with high IOP the blood viscosity would be expected not to differ much from normal values, because in these patients the high IOP is a far more important factor.

To test this hypothesis we performed blood viscosity measurements on patients at the two extremes of the IOP spectrum and compared these with measurements from controls. We also measured several determinants of blood viscosity.

Patients and methods

Eighty-three unselected patients with LTG and 23 POAG-patients with HTG attending the Eye Departments of the Academic Medical Centre and the St Lucas Hospital were investigated after they had given informed consent. In both groups diagnostic criteria for inclusion were an open anterior

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chamber angle, glaucomatous visual field changes (except in one group suspected of having glaucoma; see below), and glaucomatous disc cupping. Patients with LTG had mean diurnal IOP values of 17 mmHg (maximum 26 mmHg), while those with HTG had at least one IOP reading above 40 mmHg in a diurnal curve. The LTG group was further subdivided into three groups according to previously defined criteria[25]: a focal ischaemic subgroup (FILTG), a senile sclerotic subgroup (SSLTG), and a miscellaneous subgroup (LTG_{misc}) comprising patients not fitting into either the FILTG or the SSLTG subgroups. In short, criteria for FILTG included an optic disc with local excavation of the neural tissue rim and unipolar vertical elongation, usually with corresponding local peripapillary atrophy; those for SSLTG included a sloping excavation in a pale disc with a moth-eaten aspect combined with extensive choroidal sclerosis and peripapillary atrophy. Patients suspected of having senile sclerotic low-tension glaucoma (SSLTS) had characteristics similar to SSLTG except that they lacked visual field defects.

These groups were compared with 50 controls consisting of ophthalmic patients with normal IOP, normal disc, and normal visual field, who had neither inflammatory nor vascular conditions of the eye. Most controls were admitted for cataract surgery or other elective operations or visited the Outpatient Department for a driving licence examination. None of the patients or controls had any acute illness.

The medical record of all patients was studied and a full medical history was taken, with special emphasis on diseases known to be correlated with high blood viscosity. All patients were questioned about smoking and drinking habits, drug use, and all women about their menstrual cycle.

Blood samples were drawn without venous occlusion by means of a Vacutainer system with a 0·8 mm (21 gauge) needle. Viscosity measurements were done on blood anticoagulated with dry EDTA (1 mg/ml) within five hours of sampling. The measurements were carried out with the Contraves Low Shear 30 viscometer by means of a standardised computer directed protocol described elsewhere.[26] Temperature was kept constant at 37°C. Whole blood viscosity was measured at 10 shear rates covering the entire physiological range. Plasma viscosity was measured at five shear rates, and if the values obtained showed newtonian behaviour the plasma viscosity was calculated as the mean of the five measurements. Haemoglobin, packed cell volume (PCV), and thrombocyte count were measured on a Haemalog 94 apparatus using blood anticoagulated in EDTA (1 mg/ml); in this apparatus a microcentrifuge technique is used for measurements of the PCV. Blood was anticoagulated with trisodium citrate (0·1 ml/ml) for measurement of plasma fibrinogen by a quantitative biuret method.[27] A standard photometric method was used for determination of total serum protein. Serum protein electrophoresis was carried out according to standard methods. Serum α_2-macroglobulin was estimated immunochemically.

As a normal distribution of the results could not be assumed, statistical analysis of differences between groups was performed by the Wilcoxon sum of ranks test.

Results

COMPARABILITY OF PATIENT GROUPS

The LTG group and the control group proved to be comparable with regard to several important clinical characteristics (Table 1). Differences were seen in the prevalence of diabetes mellitus and paraproteinaemia. Diabetes mellitus occurred more frequently in the controls with higher than mean blood and plasma viscosity. Exclusion of these persons from the control group would lower the mean plasma and blood viscosity values and hence would make differences between glaucoma patients and controls larger. Furthermore, no significant difference in the other parameters measured was found between controls with and without diabetes mellitus. For these reasons we did not exclude persons with diabetes mellitus from the control group.

In none of the groups did the occurrence of paraproteinaemia raise significantly the mean values of the blood or plasma viscosity.

The HTG group on the other hand did show some important differences compared with the other groups. The mean age was about 14 years lower; none of the patients gave a history of vascular disease; the consumption of alcohol and tobacco was much higher than in either the LTG or the control group (Table 2).

The mean age (±SD) of the patients in the SSLTG and SSLTS subgroups proved to be 82·1 (±5·2) years

Table 1 *Clinical features in patient groups*

	Controls	*LTG*	*HTG*
Number	50	83	23
Age ± SD (yr)	74·7 (8 9)	73·9 (10·3)	60·6 (7·7)
Males	19	35	14
Hypertension (%)	27	30	20
Diabetes mellitus (%)	23	9	8
Ischaemic vascular disease (%)	25	20	0
Chronic pulmonary disease (%)	8	8	4
Venous thrombosis (%)	10	10	8
Paraproteinaemia (%)	2	7	8

Table 2 *Drug use, smoking, and drinking habits in patient groups*

	Controls	*LTG*	*HTG*
B-blockers (%)	12	10	8
Diuretics (%)	27	23	16
Other antihypertensives	8	12	10
NSAID (%)	12	13	4
Coumarins (%)	10	15	0
Oral contraceptives (%)	0	0	4
Smokers (%)	14	18	74
Cigarettes/week pp	30	55	70
Drinkers (%)	33	48	72
Glasses per week per patient	8	8	10

NSAID=non-steroidal anti-inflammatory drugs.

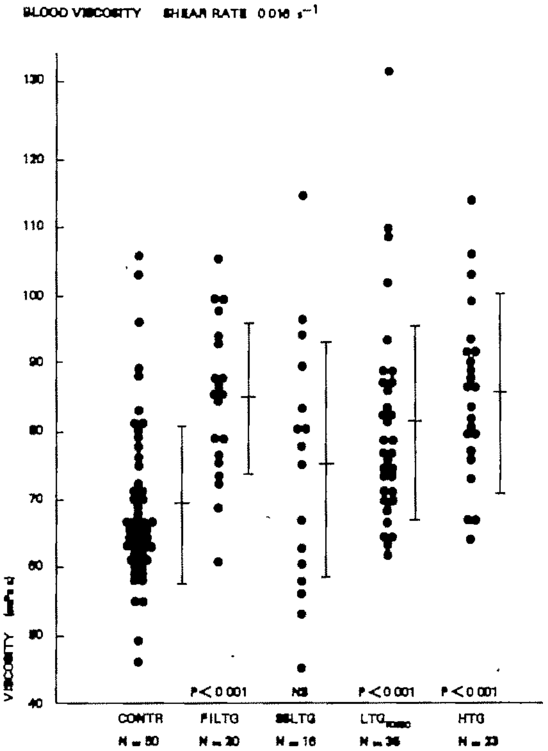

Fig. 1 *Whole blood viscosity results in patient groups and controls at the lowest shear rate measured. Mean, standard deviation, and p value for difference from controls are indicated.*

and 79·0 (±11·8) years respectively, significantly higher than controls. We therefore compared these two subgroups with a subgroup of controls of about the same age (mean age 82·8±4·0 years, n=21). The other two LTG subgroups were comparable in age with the control group (73·9±9·0 years and 70·9±10·1 years for FILTG and LTG$_{misc}$ respectively).

MEASUREMENT RESULTS

Blood viscosity at 10 shear rates was significantly higher than controls in both the HTG group and the LTG group as a whole. In the LTG group only the focal ischaemic subgroup showed significant differences over the whole range of shear rates (Table 3). Mean whole blood viscosity in the FILTG subgroup was 22% higher than in controls at the lowest shear rate and 10% at the highest shear rate. The LTG$_{misc}$ subgroup differed significantly from controls at nine shear rates, but the differences were less than in the FILTG subgroup. The SSLTG and SSLTS subgroups did not show any significant difference from a subgroup of controls of about the same age at the 10 shear rates measured, even though values in the latter were somewhat lower than in the control group as a whole.

In all groups the greatest differences were at the low shear rates. Figs. 1 and 2 illustrate the viscosity results at the lowest and the highest shear rates measured respectively.

Table 3 *Blood viscosity at 10 shear rates in patient groups and controls Values are means ± standard deviation, expressed in mPa s (1 mPa.s=1cP)*

Shear rate (s^{-1})	*Controls (n=50)*	*Total LTG (n=83)*	*FILTG (n=20)*	*SSLTG (n=16)*	*SSLTS (n=8)*	*LTG$_{misc}$ (n=35)*	*HTG (n=23)*
0·016	69·6±12.0	80·1±14·5***	84·7±11·5***	75·8±17·2	80·8±16·2*	80·8±14·2***	85·2±14 3***
0·040	56·2±10·0	64 9±11·4***	68 4±8·9***	61 9±13·5	65·2±14·0*	65·2±11·0***	68 2±9·8***
0·101	40·9±7·5	47 4±8 5***	50·2±6·6***	45·1±10·1	47·5±10·2*	47 4±8·4***	50·0±6 9***
0·255	28·4±5·3	32·9±6 0***	34 9±4·6***	31·6±7·2	32·9±7·1*	32 7±6·0***	34·9±4·9***
0·640	19·3±4 1	22 2±4·6***	23·3±3·4***	21·9±5 5	22·3±5·9	22 0±4·7**	23 3±3·4***
1·607	13 3±2·9	15·1±3 0***	15 9±2·2***	14·8±3·5	15·2±3·6	15·1±3·1**	15·9±2 3***
4·037	9·6±1 9	10 9±2·0***	11·3±1·4***	10·7±2·2	11·0±2 4	10·8±2·1**	11·4±1·5***
10 142	7 2±1·3	8·0±1·3***	8 3±0·9***	7·9±1·4	8·1±1·6	8·0±1·3**	8 3±1·0***
34·629	5 4±0 7	5 8±0·7**	5·9±0·5**	5 7±0·8	5 8±0·9	5·7±0·8	6·0±0·5***
118·242	4·2±0·5	4·5±0 5**	4·6±0·4**	4·4±0 6	4·5±0·7	4·5±0 6*	4 6±0·4**

*p<0·05 (vs controls, Wilcoxon test).
**p<0·01 (vs. controls, Wilcoxon test)
***p<0·001 (vs controls, Wilcoxon test)

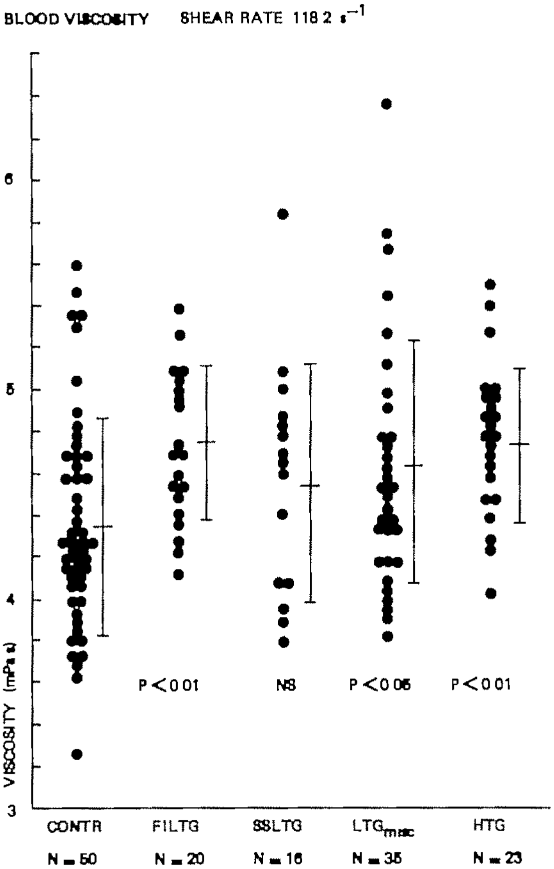

Fig. 2 *Whole blood viscosity results in patient groups and controls at the highest shear rate measured. Mean, standard deviation, and p value for difference from controls are indicated*

Mean plasma viscosity was significantly higher than in controls in the LTG group but not in the HTG group. Again within the LTG group a statistically significant difference was evident only in the FILTG and LTG$_{misc}$ subgroups (Fig. 3). The packed cell volume was significantly higher in both the LTG and the HTG group than in the controls; in the LTG group the higher level was confined to the FILTG and LTG$_{misc}$ subgroups (Fig. 4).

As to the other parameters measured, including plasma fibrinogen and α_2-macroglobulin, no statistically significant differences between the groups were detected (Table 4).

Discussion

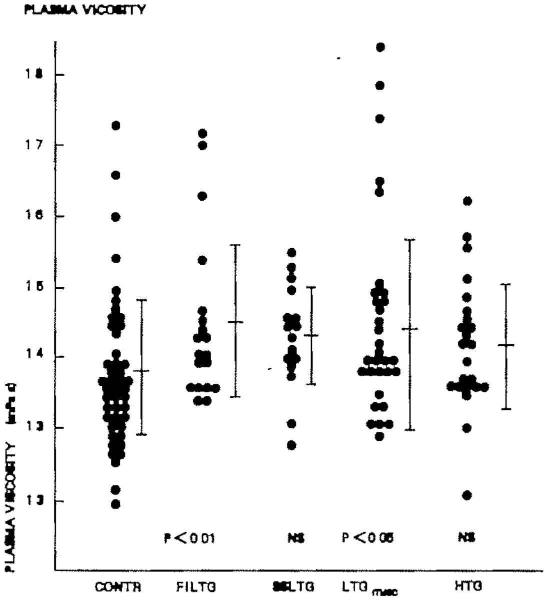

Fig 3 *Plasma viscosity results in patient groups and controls. Mean, standard deviation, and p value for difference from controls are indicated.*

This study shows that patients with LTG have a significantly higher whole blood viscosity measured over the whole range of physiological shear rates when compared with a control group matched for age, sex, and several important clinical features that influence blood viscosity. The increased viscosity was associated partly with increased packed cell volume and partly with increased plasma viscosity. It may be questioned whether a group of cataract patients is a suitable control group. The fact that the frequency of general cardiovascular disease in the LTG group and the cataract group is comparable is in favour of the selection of the cataract group as control. One could

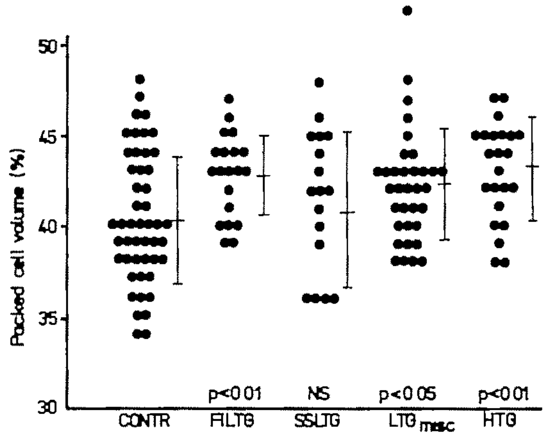

Fig. 4 *Packed cell volume results in patient groups and controls Mean, standard deviation, and p value for difference from controls are indicated.*

Table 4 *Plasma viscosity and blood, serum, or plasma concentrations of the other variables measured. Values are means ± standard deviation*

	Controls (n=50†)	*Total LTG (n=83)*	*FILTG (n=20)*	*SSLTG (n=16)*	*SSLTS (n=8)*	*HTG (n=23)*
Plasma viscosity (mPa.s)	1·38±0·10	1·43±0·12*	1·45±0·12*	1·43±0·07	1·42±0·08	1·41±0·09
Haemoglobin (mmol/l)	8·7±0·79	9·0±0·80*	9·2±0·46*	8·9±1·04	8·8±0·81	9·4±0·74*
Haematocrit (%)	40·3±3·59	41·9±3·27*	42·8±2·20**	40·8±4·26	40·6±4·18	43·1±2·95*
Fibrinogen (g/l)	2·74±0·59 (n=17)	2·77±0·84	2·80±0·70	2·98±0·68	2·73±0·60	2·89±0·86
α_2-macroglobulin (g/l)	3·11±1·03	3·06±0·70	3·11±0·72	3·06±0·93	3·22±0·87	2·64±0·83
Total serum Protein (g/l)	67·7±5·7	70·2±4·9	70·2±4·1	71·7±3·9	69·3±4·5	70·3±4·9
Albumin (g/l)	39·3±2·7	41·1±5·1	41·8±3·4	41·0±2·3	40·8±2·0	41·4±2·7
α_1-globulin (g/l)	2·16±0·44	2·23±0·59	2·20±0·62	2·37±0·52	2·29±0·32	2·28±0·53
α_2-globulin (g/l)	6·93±1·39	7·13±1·41	7·31±1·36	7·62±1·09	7·11±1·48	7·34±1·54
β-globulin (g/l)	7·65±1·07	7·92±1·29	7·86±1·08	8·28±1·27	7·66±1·38	8·08±1·58
γ-globulin (g/l)	11·7±4·0	11·3±3·2	11·1±3·12	12·4±2·32	11·3±2·61	11·5±3·4
Thrombocytes (× 10^9/l)	233±46	250±60	259±65	241±37	237±80	281±82

†Only 17 control values of fibrinogen were available
*$p<0·05$ (vs controls, Wilcoxon test)
**$p<0·01$ (vs. controls, Wilcoxon test).

argue that cataract is an eye disease that may in itself be related to viscosity. Even if this were so the outcome would be influenced only in a negative way. One would then expect the differences between LTG and a completely normal age matched group to be even greater. We were unable to show a difference in whole blood viscosity between LTG and HTG patients. In fact the HTG patients in our study had whole blood viscosity values similar to those of the LTG subgroup with the highest blood viscosity results. The high blood viscosity in the HTG group was not associated with increased plasma viscosity, and a high packed cell volume appeared to be the dominant factor involved. This may be explained by the large tobacco consumption in the HTG group as compared with the other groups. Owing to this difference in smoking habits in our series a valid conclusion as to the original hypothesis, namely, that blood viscosity in LTG patients will be higher than in HTG patients, cannot be drawn.

These results are suggestive of increased whole blood viscosity being a risk factor for glaucomatous optic nerve damage in at least some patients with LTG, notably those subclassified by us as belonging to the focal ischaemic subgroup. It is interesting that two subgroups of LTG could be identified by ophthalmoscopy that show significant differences in blood viscosity. Without a subclassification of LTG these differences would have been overlooked. This emphasises the necessity of subclassification in research into the pathogenesis of LTG. There is evidence that local disturbance of the microcirculation at the disc is an important damaging factor in FILTG. Fluorescein angiography in these patients frequently shows inferotemporally localised, sharply defined filling defects of the optic disc, while the remainder of the disc appears well vascularised.[28] From a theoretical point of view the role of high blood viscosity, especially at low shear rates, in the pathogenesis of glaucomatous optic nerve damage would be obvious.

In normal circumstances the major factors in the microcirculation are the autoregulation of the vascular diameter and the perfusion pressure, blood viscosity playing a minor role. However, blood is a fluid with non-newtonian behaviour, which implies that blood viscosity varies with the force applied to it. The rheological term 'shear rate' is often used in this context, high shear rate being present when flow is fast and the vessel diameter small, and low shear rate present when flow is slow and the vessel has a large diameter. The non-newtonian behaviour of blood is due to the tendency of red cells to aggregate at low shear rates when low shear forces are applied to them, while these aggregates disperse when the shear forces become higher. Furthermore, when shear rates are high the red cells are deformed to become optimally adapted to the flow conditions. Normally in the capillaries high shear rates occur and blood viscosity will be low, but, as flow is chronically retarded, irrespective of the causative factor shear rates will fall and blood viscosity will rise, resulting in still further decreasing flow. Thus when vasomotor reserve becomes exhausted, even slightly increased viscosity may become a critical and limiting factor governing flow.[29]

There is evidence that increased blood viscosity plays a role in capillary non-perfusion associated with retinal vein occlusion[23,24] and diabetic retinopathy.[20-22] The angiographic findings in FILTG patients suggest localised capillary non-perfusion of the disc. The fact that there is a predilection for the inferotemporal margin of the disc may be due to some anatomical peculiarity of the vascularisation to that area. According to the above theoretical considerations patients with increased blood viscosity would be at great risk of developing decompensation of the microcirculation, viscosity not being the initiating but an aggravating factor, setting into motion a vicious circle of decreasing flow, which leads to higher viscosity, which then further slows down flow, and so on.

In the senile sclerotic LTG subgroup, in which no increase of blood viscosity could be demonstrated, senile atrophy probably owing to generalised vascular disease was proposed earlier as a pathogenic mechanism.[25] The same goes for the SSLTG subgroup.

Finally the LTG_{misc} subgroup, which is a collection of patients that could not be classified into either the FILTG or the SSLTG subgroup, has viscosity values that lie in between those for FILTG and SSLTG, possibly reflecting its heterogeneity.

Prospective studies are needed to establish more clearly the role of high blood viscosity in the development of glaucomatous optic nerve damage. If a causative role of high blood viscosity can be demonstrated, this finding would have therapeutic consequences, since several drugs have been shown to be effective in lowering blood viscosity.

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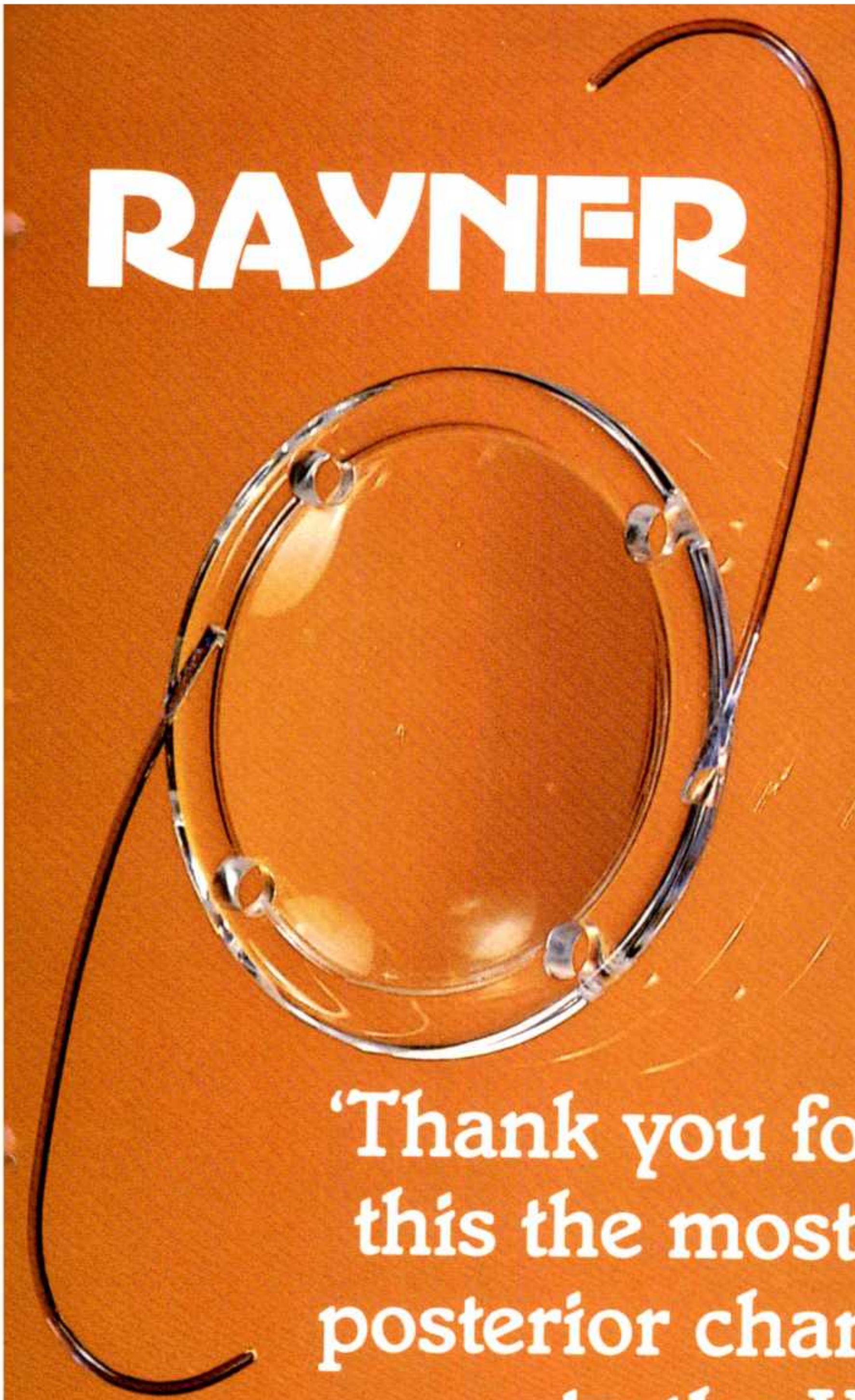

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hours the dosage may be safely increased to 2 drops every hour. Care should be taken not to discontinue therapy prematurely.
ntra-indications, Warnings, etc. CONTRA-INDICATIONS. Acute superficial herpes simplex keratitis. Fungal diseases of ocular
ructures. Vaccinia, varicella and most other viral diseases of the cornea and conjunctiva. Tuberculosis of the eye. Hypersensitivity
the constituents of this medication. **Warnings** Steroid medication in the treatment of herpes simplex keratitis (involving the
romal requires great caution; frequent slit-lamp microscopy is mandatory. Prolonged use may result in glaucoma, damage to the
tic nerve, defects in visual acuity and fields of vision, posterior subcapsular cataract formation, or may aid in the establishment of
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armaceutical Precautions Protect from freezing. **Legal Category** POM. **Package Quantities** Supplied in plastic dropper
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During the initial 24 to 48 hours, the dosage may be safely increased to one drop every hour. Care should be taken not to di
treatment prematurely. Shake well before using. **Contra-indications, Warnings etc.** Acute untreated purulent ocular infe
Acute superficial herpes simplex (dendritic keratitis), vaccinia, varicella and most other viral diseases of the conjunctiva an
Ocular tuberculosis, fungal diseases of the eye and hypersensitivity to any of the components of the drug. **Warnings** As fo
above and, in addition in diseases due to micro-organisms resistant to neomycin, infection may be masked enhanced or ac
the steroid. Prolonged use may result in overgrowth of nonsusceptible organisms. Articles in current medical literature in
increase in the prevalence of persons sensitive to neomycin. The possibility of such a reaction should be borne in mind. If s
or other untoward reactions occur discontinue the medication. **Precautions** Patients with histories of herpes simplex ke
should be treated with caution. Use of topical steroids may increase intraocular pressure. Safety of intensive or protracte
topical steroids during pregnancy has not been substantiated. Local side effects of steroid therapy, ie skin atrophy, striae a
telangiectasia, are especially likely to affect facial skin. **Pharmaceutical Precautions** Shake well before using. Do not fre
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British Journal of Ophthalmology, 1985, **69**, 771–773

Early intraocular pressure response following laser trabeculoplasty

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SUMMARY The early response in the intraocular pressure following laser trabeculoplasty was investigated in 38 patients. An increase in pressure was found in 16 patients (42%), of whom eight had a moderate (<9 mmHg) and eight a severe (>10 mmHg) increase. The maximum increase was recorded during the first post-laser hour in 13 patients (34·2%) and at 4 h in three patients postoperatively. A routine follow-up observation at 4 h after laser treatment is recommended to prevent 'silent' hypertensive risk.

Laser trabeculoplasty (LTP) has become a major tool for the treatment of open-angle glaucoma. A high rate of success has been reported by most investigators,[1-3] with only minor complications. A raised intraocular pressure (IOP) during the first three weeks following surgery has been reported to be the most serious complication and may lead to further field loss.[2,4,5] The increase in IOP is unpredictable and its prognosis for the individual eye or the success rate of the treatment is not clear.[3,5] We studied the changes in IOP during the first 24 hours following laser treatment in order to establish an immediate follow-up regimen after LTP.

Material and methods

Thirty-eight patients with uncontrolled open-angle glaucoma, 22 males and 16 females, aged 58 to 81 (mean age 62) were included in the study. All the patients were under antiglaucomatous medical treatment, and the visual fields were abnormal in every case. Laser trabeculoplasty was applied to each patient on one eye by means of the Coherent Radiation Argon Laser Unit A900. Eighty to 100 spots were applied at the pigmented trabecular meshwork throughout 360° of the angle circumference. The IOPs were measured before treatment and ½ hour, 1 hour, 4 hours, and 24 hours after LTP. Postoperatively all patients carried on their initial antiglaucomatous medications with additional dexamethasone three times a day. Patients with severe glaucomatous damage in which the IOP increased over 10 mmHg from the initial level were treated with glycerol 50% by mouth or mannitol 20% intravenously.

Results

During the first 24 hours following LTP the intraocular pressures increased by 3·15 mmHg mean value in 16 out of the 38 treated patients (42%). Five patients (13%) had no change in their IOP, and in 17 (45%) the IOP was reduced by 3 to 24 mmHg. The pressure increase was moderate (<9 mmHg) in eight patients (21%) and severe (>10 mmHg) in the remaining eight patients (21%) (Table 1). The maximum increase in IOP was observed during the first postoperative hour in 13 out of the 16 patients. In another patient the IOP continued to increase to maximum levels at 4 hours postoperatively, and in the remaining two cases a rise in IOP was first noted at 4 hours after LTP (Table 2). Over all patients the mean of the pressures at 24 hours was significantly reduced as compared with the prelaser levels ($p<0{\cdot}001$ by Student's *t* test). In two patients (5·2%) a moderate (<9 mmHg) increase in IOP was recorded,

Table 1 *Early IOP variations in the 38 patients during the first four hours*

	No of patients	*%*
IOP ≤ pretreated levels	22	58
IOP increase ≤ 9 mmHg	8	21
IOP increase ≥ 10 mmHg	8	21
Total	38	100

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Table 2 *Initial and maximum IOP increase in 16 patients during the first four hours after LTP*

Time	*Initial pressure rise (mmHg)*		*Maximal pressure rise (mmHg)*	
	No of patients	*Mean±SD*	*No of patients*	*Mean±SD*
½ h	9	6 0±3 28	4	7·25±4·7
1 h	5	6 4±2 82	9	9 55±4·1
4 h	2	11	3	10±5·29

Table 3 *Pressure changes in eight patients with moderate increase of IOP (<9 mmHg)*

	Before LTP	*IOP (mmHg), 30–60 min after LTP*	*4 h after LTP*	*24 h after LTP*
Case 1	23	32	20	16
Case 2	28	32	29	17
Case 3	22	30	26	19
Case 4	26	30	27	20
Case 5	23	30	26	16
Case 6	24	27	22	16
Case 7	28	32	32	24
Case 8	26	30	28	20

and in only one patient the pressure during the first 24 hours following LTP could not be controlled by intravenous mannitol, so that surgical intervention was required. Table 3 demonstrates pressure changes in the group with moderate postlaser pressure increase (<9 mmHg). As shown in this table, in six out of the eight patients the peaks present at the first postoperative hour had dropped by 4 h and remained as such thereafter. In the other group of eight patients (23·6%) who had a severe increase in IOP (>10 mmHg) a single dose of hyperosmotics was required to control the pressure.

Mild anterior uveitis was observed in all the cases. The severity of the inflammatory process did not correlate with the IOP levels.

Discussion

All investigators have agreed that an acute increase of IOP may lead to further deterioration of visual field in a glaucomatous eye. Therefore it is of high importance to investigate the timing and levels of such pressure elevation which may occur as a 'silently' during the first 24 hours postoperatively and thus prevent the risk. In our series of 38 patients 16 (42%) had an increase in IOP following LTP. This finding is in keeping with those of other studies.[1-8] Krupin *et al.*[6] in a similar study reported that more than 50% of their patients had an increased IOP over prelaser mean values, but in only 14% was additional medical therapy required. Hoskins *et al.*[4] reported an increase in IOP in 34% of his patients and persistently raised tension over 24 hours in 6% only. As results reported here show, 13 of the patients (34·2%) had a maximum increase in IOP already during the first postoperative hour. This is similar to Krupin *et al.*'s study,[6] which concluded that the IOP should be followed up for 1–2 hours postoperatively and those patients who have a clinically significant increase should be followed up for at least 24 hours.

According to our findings, in agreement with those of Weinreb *et al.*,[7] if the raised pressure had declined from its peak after that period, a further increase was unlikely. However, attention should be drawn to the three patients in our series who had a maximum rise in IOP only four hours after LTP. In two of those it was first recorded at 4 h post laser treatment. Therefore it is suggested that routine follow-up should be extended to four hours postoperatively. Furthermore, in another study a routine six hours' follow-up was suggested.[7] On an outpatient regimen such a long follow-up might be inconvenient, but our findings suggest it should be considered.

Various factors may be associated with the acute increase in IOP. A post-LTP inflammatory response is one of them. Post-LTP iritis was observed in all our patients, but we could not correlate the increase in IOP with the inflammatory response. The inflammation may be mediated by prostaglandins or other endogenous hormones.[9,10] It may therefore be reasonable to assume that fewer burns given to the trabecular angle will induce less inflammatory response and will be associated with less IOP elevation. This line of thought was established by Wilensky and Weinreb,[3] who applied only 25 spots at 90° of the angle circumference. In their series only 2 out of 21 patients had an IOP increase of over 10 mmHg.

In our study the laser spots were targeted at the mid-trabeculum and resulted in pressure increases considerably higher than those in the reports in which the laser was applied to the anterior trabeculum.[5,8,11]

In summary, we suggest a four-hour regimen of postoperative follow-up. longer evaluation and/or treatment are required if the IOP remains significantly raised

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Clostridium septicum panophthalmitis with systemic complications

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SUMMARY A fulminant case of endophthalmitis due to *Clostridium septicum* is described. The patient presented with spontaneous gas gangrene panophthalmitis, with early visual loss and an air bubble in the anterior chamber. Death ensued, and necropsy revealed changes consistent with severe arterosclerotic cardiovascular disease, a relationship not uncommon in patients with clostridium sepsis. This association as well as the histopathology of the globe are discussed.

Gas gangrene panophthalmitis is a rare condition usually following penetrating injury to the globe. In most of the reported cases the infecting organism has been *Clostridium perfringens*.[1-4]

Characteristic findings are brawny swelling of the lids, coffee coloured discharge, hypopyon, ring abscess of the cornea, gas bubbles in the anterior chamber, and early loss of vision. Systemic manifestations include fever and leucocytosis, malaise, nausea, and vomiting. Treatment generally consists of evisceration or enucleation of the globe and systemic antibiotics. Extraocular extension of infection is prevented by well timed surgical intervention.

To the best of our knowledge, this paper is the first report of gas gangrene panophthalmitis due to *Clostridium septicum*.

Case report

A 78-year-old Caucasian woman was admitted to hospital on 15 October 1981 with a 24-hour history of nausea, vomiting, and mild abdominal pain. The diagnosis on admission was dehydration and acute gastroenteritis. There was a history of atherosclerotic heart disease and degenerative arthritis Vital signs at the time of admission showed a blood pressure of 152/80 mmHg, respiration rate of 20/min, a slight tachycardia, and a temperature of 101°F (38·3°C) Examination revealed a slightly obese Caucasian woman who was vomiting and complaining of abdominal pain. The heart and lung examination was normal. The abdominal examination revealed tenderness but good bowel sounds. The white cell count was 28·9×10^9/l, the haemoglobin was 13·7 g/dl, and the packed cell volume was 40·1%

Later on that evening the patient became confused and hypotensive and had a respiratory arrest. She responded to cardiorespiratory resuscitation and was transferred to the intensive care unit The differential diagnosis at that time included a myocardial infarction and gastrointestinal haemorrhage. A serous discharge was noted from the right eye, and lid and conjunctival specimens were taken for culture Erythromycin 500 mg intravenously six hourly was added to the cefamandole begun on admission.

Two days after admission while the patient was on a ventilator her temperature spiked to 104·6°F (40·3°C) and blood cultures were obtained. A heart and a perfusion lung scan were performed, and both were within normal limits. An ophthalmology consultation was obtained, at which time a gas bubble was noted in the anterior chamber

Ophthalmic examination on 18 October 1981 revealed an opaque cornea and a very tense globe An anterior chamber paracentesis was performed and approximately 0·10 ml of chocolate coloured fluid was obtained. This material was plated on blood and chocolate agars and was submitted for anaerobic culture.

On 19 October 1981 the patient died. A general necropsy, performed 2½ hours after death, revealed severe atherosclerotic cardiovascular disease, dissecting aortic aneurysm, severe brochopneumonia, and changes consistent with sepsis. The aortic aneurysm was not ruptured and did not appear to be

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the cause of death. No recent myocardial infarction was found. Culture of the anterior chamber aspirate grew a pure colony of *Clostridium septicum*.

PATHOLOGICAL EXAMINATION OF THE EYE

The globe was examined under the dissecting microscope in the pathology laboratory. No penetrating injury could be identified. The corneal surface was opaque, extremely irregular, and thin in the centre. On transverse sectioning the globe was observed to be diffusely necrotic. A small amount of purulent, coffee coloured fluid was found in the anterior chamber and vitreous cavity. The inner surface of the eye was pale and extensively necrotic. The retina was not identified. Instead the inner surface of the globe was irregular, elevated, and bullous in appearance.

Histological examination of the eye showed that all ocular tissues were involved in an acute necrotising inflammatory process (Fig. 1). The cornea and sclera (Fig. 2) were diffusely infiltrated with acute inflammatory cells and had undergone severe collagen degeneration and necrosis. Scleral and episcleral blood vessels were surrounded by acute inflammation and their walls were partially necrotic. The central cornea was extremely thin, with total absence of the epithelium and more than half of the stroma. The ciliary body and iris were extensively inflamed and necrotic. The choroid was detached in some segments and was also involved in the diffuse necrosis; in some areas only the framework of the vasculature was left intact. The choroidal blood vessels were found to contain many thromboemboli (Fig. 3). Only fragments of retinal structures showing severe necrosis could be identified in certain segments of the globe. In addition to its necrotic appearance the tissue contained empty spaces possibly secondary to gas-producing bacteria. The overall bullous appearance of the retina and choroid was also consistent with extensive oedema and gas production. A few clusters of Gram-positive bacteria were identified, but these did not have the spindle, drumstick appearance of *Clostridium septicum* and did not contain spores.

Discussion

Clostridial infections of the eye are devastating. Since Leavelle's[1] extensive review of 53 previously reported cases as well as three of his own nine additional cases have been reviewed by Frantz *et al.*[5] All previously reported cases of gas gangrene panophthalmitis followed pentrating injuries to the eye and the offending organism was *Clostridium perfringens*. Frantz and colleagues' report included a 68-year-old white male who presented with fever, pain in the right upper quadrant of the abdomen, and panophthalmitis of the left eye. Unlike the previously described cases their case resulted from endogenous infection of the eye complicating perforation of a gangrenous gallbladder.

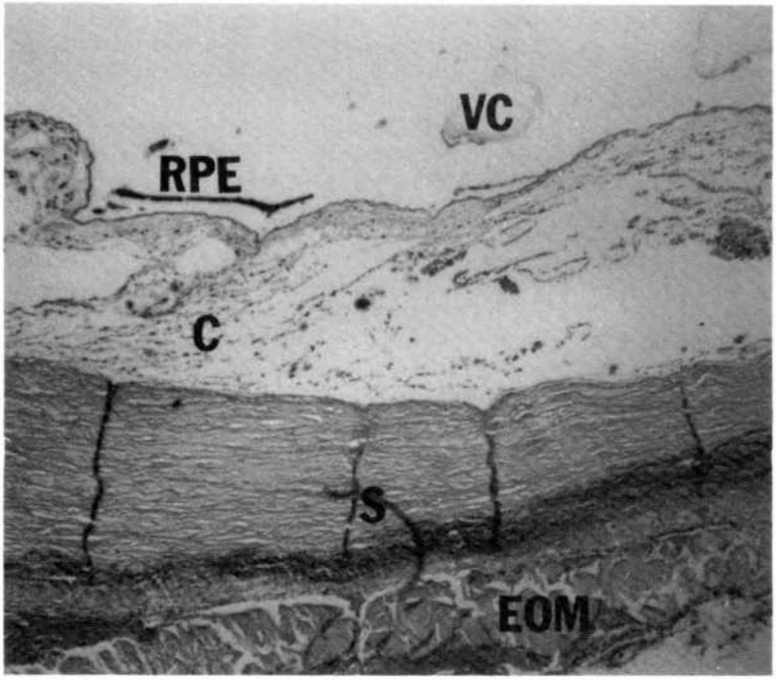

Fig. 1 *Extensive oedema and necrosis of retina and choroid. Retina is totally necrotic. Only a short segment of detached retinal pigment epithelium* (RPE) *is seen in the figure.* VC: *vitreous chamber;* C: *choroid;* S: *sclera;* EOM: *extraocular muscle. (Haematoxylin and eosin, ×40).*

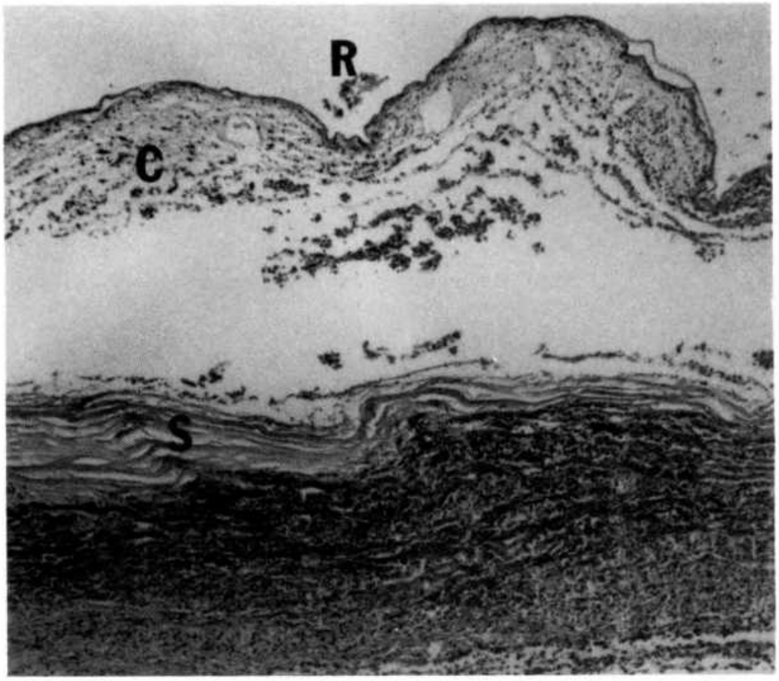

Fig. 2 *Diffuse infiltration of acute inflammatory cells and necrosis in retina* (R), *choroid* (C), *and sclera* (S). *(H and E, ×100).*

The clinical picture of clostridial panophthalmitis described by Leavelle is one of severe pain and rapid loss of vision within 12 hours of injury. An explosive panophthalmitis with chemosis and swelling of the lid is usually apparent by 18 hours. Hypopyon, ring abscess of the cornea, coffee coloured discharge, gas bubbles in the anterior chamber, immobilisation of the globe, and a total loss of fundus reflex with loss of vision were signs usually evident by 24 hours. Conventional antibiotic therapy has been entirely impotent against this disastrous disease, even though some cases were seen very early.

For practical purposes the clostridia may be divided into three groups: *C. botulinum* causing botulism, *C. tetani* causing tetanus, and several types of clostridia causing gas gangrene, commonly *C. perfringens, C. novyi, C. septicum, C. histolyticum,* and *C. fallax*. All the clostridia are large Gram-positive rod-like anaerobic bacteria with a larger spore-forming end, giving them a drumstick appearance. The clostridia which may be considered as potential causes of gas gangrene panophthalmitis produce powerful exotoxins. The most common member of this group of organisms is *C. perfringens (C. welchii)*; next are *C. novyi* and *C. septicum* in degree of frequency of isolation from war wounds.

C. septicum, an obligate anaerobe, is ß-haemolytic on blood agar and highly motile. Spreading growth can be overlooked, as isolates may form only a thin film on the culture plate without the definition of distinct colonies. Smears from cultures show Gram-positive sporulating rods with oval terminal and subterminal spores. *C. septicum* is differentiated from other clostridia by its carbohydrate fermentation reactions and its lack of lecithinase or lipase production.

An association of clostridial infections with malignancy, especially cancer of the colon, has been demonstrated by several case reports.[6-9] In 1969 Alpern and Dowell[6] reported that 23 of 27 patients (85%) with *C. septicum* infections whose cultures were referred to the Center for Disease Control (CDC) for identification had malignant disease. Of the four patients who did not have malignant disease three developed intestinal tumours one to two months after the *C. septicum* was cultured.

Koransky *et al.*[7] reported on the clinical significance of *C. septicum* bacteraemia. The medical records of 59 patients were reviewed; 42 (71%) of these patients had malignant disease. Half had haematological malignant disease and one half had solid tumours. Of the 21 patients with solid tumours 14 (67%) had cancer of the colon. The caecum and distal ilieum were thought to be the most probable portals of entry for *C. septicum* bacteraemia among the 28 patients examined at necropsies. They reported one patient with distant metastatic infection

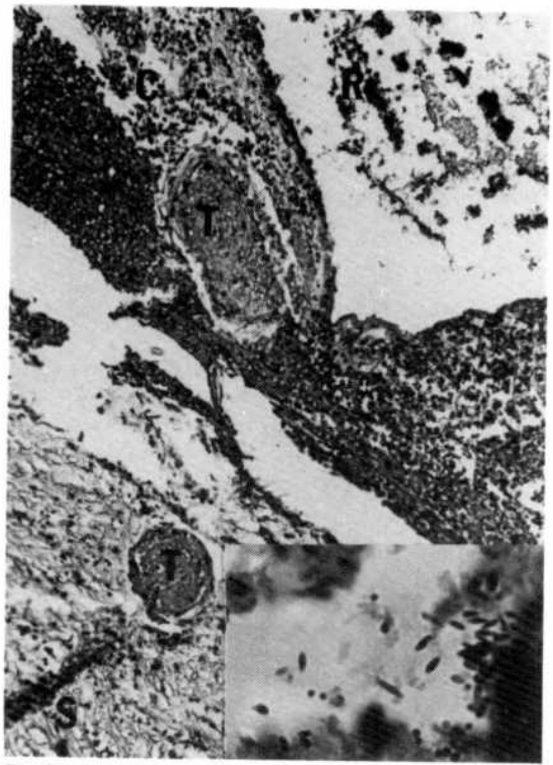

Fig. 3 *Oedema, necrosis, and diffuse acute inflammatory cell infiltration of the retina, choroid, and sclera with multiple thromboemboli* (T) *in choroidal and scleral blood vessels.* R: *necrotic retina;* C: *choroid;* S: *sclera. (H and E, ×85).* Insert: *Organisms, identified in culture as* Clostridium septicum, *within necrotic areas of the sclera. (Gram stain, ×850, oil immersion).*

of the eye who had an enucleation and then was later found to have adenocarcinoma of the colon.

Further results of their study showed that of the 17 patients with no detectable malignancy six had severe atherosclerotic cardiovascular disease with a gangrenous extremity or gangrenous bowel. Infection with *C. septicum* was the apparent cause of death in 40 patients (68%). All surviving patients were given penicillin, cephalothin, chloramphenicol, or carbenicillin (antibiotics to which clostridia have been found to be sensitive[10]) soon after they were admitted to the hospital.

Post-mortem examination of our patient, who apparently developed spontaneous gas gangrene panophthalmitis due to *Clostridium septicum*, failed to disclose an occult malignant tumour, which must be ruled out when *C. septicum* is cultured from a 'metastatic' infection outside the bowel.[6] However, she did have severe atherosclerotic cardiovascular disease, as did six of 17 patients without malignant disease in Koransky and colleague's series.[7] It has been suggested that arteriosclerosis may have a role in the development of ischaemia and tissue necrosis, which are important predisposing factors for clostridial growth and gangrene formation.[7]

Although a positive (ante-mortem) blood culture was not obtained in our case, we attribute this to antimicrobial therapy instituted prior to the sampling. Fever, especially when accompanied by gas gangrene, tissue necrosis, and/or the signs of shock which characterised our patient's hospital course, should suggest possible septicaemia caused by toxic bacteria such as clostridium.

The importance of early recognition and prompt therapy in patients with *Clostridium septicum* infection cannot be overemphasised. When these patients are admitted to hospital they are acutely ill and toxic. Their clinical course is usually fast downhill, and unless the appropriate antibiotics are administered soon after admission the outcome is fatal. Blood cultures, both aerobic and anaerobic, should be performed rapidly, and therapy should be instituted before the results of the cultures are received. Penicillin remains the drug of choice, but some patients may be treated successfully with chloramphenicol, carbenicillin, or cephalothin.

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Acanthamoeba keratitis successfully treated medically

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SUMMARY The first medical cure of a corneal infection due to an *Acanthamoeba* species is reported. The 44-year-old patient developed a suppurative keratitis associated with an epithelial defect, hypopyon, and secondary glaucoma. Acanthamoeba was confirmed as the causative agent four months after presentation when positive cultures were obtained from the cornea and from the conjunctiva. Sensitivity studies of the isolated organism were performed, and the infection was successfully controlled by treatment with a combination of dibromopropamidine and propamidine isethionate ointment and drops and neomycin drops. Keratoplasty was performed 22 months after onset, and no viable acanthamoebae were present in the resected tissue, though possible cyst remnants were identified by immunofluorescent techniques.

Infection of the eye with *Acanthamoeba* species has been reported many times[1-7] and has been associated with a fatal meningoencephalitis.[2] These infections are difficult to recognise and treat,[8] and acanthamoeba is usually considered only after failure of conventional treatment for more common causes of suppurative keratitis. No medical cure has yet been reported, and the outcome of all cases has been very poor, with excisional keratoplasty as the most successful diagnostic and therapeutic measure.

Case report

CLINICAL PRESENTATION

The patient was a 44-year-old meat porter, physically very fit and a marathon runner. In April 1979 he was splashed in the right eye with blood from a condemned carcass of meat but did not suffer any direct trauma to the eye. Within a few days the eye became red and sore and a variety of topical medicaments were given by the patient's general practitioner and local ophthalmologist including mydriatics, aureomycin, gentamicin, and neomycin with corticosteroid drops. Because of continuing deterioration the patient was referred to Moorfields Eye Hospital, where in June the findings were of a suppurative keratitis, hypopyon, and secondary glaucoma without any distinctive features. Corneal and conjunctival cultures and smears showed no organisms and no growth in any media but only pus cells and debris. A slow improvement in the signs followed subconjunctival and topical gentamicin, mydriatics, and topical dilute steroids with acetazolamide to control the intraocular pressure. The improvement was not maintained, and on several occasions the hypopyon increased for no obvious reason and then regressed again on continued treatment. This relapsing course continued for several months and in September the corneal epithelium broke down, with increasing stromal suppuration and hypopyon, producing an appearance similar to that seen in a patient subsequently shown to have acanthamoeba infections. Smears continued to show only pus cells and debris with no organisms. But special cultures for acanthamoeba from both cornea and conjunctiva grew *Acanthamoeba* sp. identified morphologically as *A. polyphaga* and continued to be positive for some days (Table 1). Nasal and pharyngeal cultures for acanthamoeba were also taken frequently and were all negative, as were cultures from the unaffected left eye.

CULTURE TECHNIQUE

Petri dish plates were prepared with 1·5% Oxoid L28 agar, allowed to set, and left overnight at room temperature. *Aerobacter (Klebsiella) aerogenes* was grown in trypticase-soy broth or on nutrient agar, and the bacteria were washed by centrifugation three

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times in phosphate-buffered saline (PBS). The bacterial pellet was resuspended to give a milky suspension in distilled water and stored (up to three months) at 4°C. Two to three drops were spread on the agar plates, allowed to absorb at 37°C, and the patient's samples were inoculated directly on to the surface of the plates. They were incubated at 37°C in a moist atmosphere for up to three days, and were examined for growth of amoebae by an inverted microscope. Further identification of the amoebae was by examination of trophozoites and cysts in suspension in Page's saline[9] under normal light and phase-contrast microscopy. On the basis of the presence of acanthopodia in the slowly moving trophozoite, and a polygonal double walled cyst with characteristic ostioles, the organisms were assigned to the genus *Acanthamoeba*.

TREATMENT

On the basis of previous sensitivity results from cases of acanthamoeba infection at Moorfields (discussed later) treatment was begun with drops of propamidine isethionate 0·1% hourly by day and night with dibromopropamidine ointment 0·15% four-hourly. After nine days of treatment the eye became much redder with rapidly worsening lid swelling despite improvement in corneal signs. These changes were attributed to toxicity, and since the sensitivity results for the organism cultured (Table 2) were now available treatment was changed to neomycin drops four-hourly day and night. By October the epithelium had healed, and four-hourly prednisolone drops were added, with steady improvement in the corneal inflammatory signs. The treatment was slowly reduced until the patient was using only neomycin drops four times daily. These were continued for one year, at which time limbal follicles developed with some increased palpebral conjunctival hyperaemia and cellularity but no sign of any skin irritation. All topical therapy was stopped and penetrating keratoplasty proposed, but not performed for a further four months at the patient's request for social reasons. During this period all the limbal and conjunctival signs disappeared, and no topical therapy was given.

An 8 mm penetrating keratoplasty was carried out 22 months after initial presentation. The postoperative treatment included propamidine isethionate drops four times daily in addition to the usual topical steroid and antibiotics employed. The propamidine drops were continued four times daily for two months without any evidence of adverse effect on the corneal graft or the remainder of the eye. After cessation of therapy the graft remained clear for nine months, when a rejection episode developed but was easily controlled with topical steroids. The graft remains clear at present and vision is 6/24, being reduced by lens opacities. The intraocular pressure is controlled with timolol maleate 0·25% drops twice daily.

Table 1 *Culture results*

	Right eye	
	Conjunctiva	*Cornea*
17 Sept	+	+
20 Sept	−	+
24 Sept	−	−
27 Sept	−	−
30 Sept	−	+
4 Oct	−	−
8 Oct	−	−
13 Oct	−	−
15 Oct	−	−
19 Oct	−	
23 Oct	−	
28 Oct	−	

Nasal and nasopharyngeal cultures always negative

Histological examination of the excised corneal disc showed no special changes and no signs of acanthamoeba on light or electron microscope examination. By immunofluorescent techniques against acanthamoeba specific antigens it was possible to see small curved segments which took up the stain and which probably represented portions of broken up cyst wall.

SEROLOGY

Serum was taken at the time of positive corneal and conjunctival cultures and on four occasions during the following month. A low level of antibody was present with a slight rise, but the titres were not significantly raised above levels found in 'normal' sera (Table 3). Antibody could not be detected in serum or aqueous humour at the time of keratoplasty.

Table 2 *Relative sensitivities*

	Minimal inhibitory concentrations (μg per ml)	
	IT	*AmC*
Myxin	<1·2	2·4
Paromomycin	4·9	4·9
Ziram	4·9	9·8
Bayer 1703	>39·0	>39·0
Azalomycin	9·8	>19·5
Venturicidin	>312·0	>312·0
Neomycin sulphate	7·5	39·0
DS 9073	5·0	9·8
Propamidine	<1·25	<1·25
Dibromopropamidine	<1·25	2·5

IT=inhibition of trophozoite
AmC=Amoebicidal (subculture negative)

Table 3 *Serology against acanthamoeba (Ryan strain)*

20 Sept	1/16	13 Oct	1/32
27 Sept	1/16	19 Oct	1/32
4 Oct	1/16		

Discussion

This case differs from others reported in that it was not associated with direct ocular trauma or previous corneal ulceration, acanthamoebae were recovered directly from the cornea and the conjunctival sac, and the infection was subsequently controlled by topical therapy alone.

Although acanthamoeba infections of the eye have certain characteristic features, such as a slow relapsing course with development of ring abscess, recurrent epithelial breakdown, hypopyon which waxes and wanes, and secondary glaucoma, diagnosis is difficult and often long delayed. This is due in part to the need for special culture plates of plain agar preseeded with aerobacter to encourage growth of acanthamoeba and also because the organism cannot be identified on the usual corneal scrapings and smears which are taken and air dried to fix cells and bacteria. Such air drying causes rupture of these delicate organisms, leaving no distinctive residuum, but preserves cysts where present. Spray fixative such as is used for cervical cytology and other techniques are being tried to obtain better smear preparations, which should permit earlier diagnosis. Meanwhile the studies of sensitivity of the *Acanthamoeba* species identified from this case and others seen and treated at Moorfields Eye Hospital confirm that propamidine and dibromopropamidine isethionate are the most useful therapeutic agents in addition to neomycin, which has previously been suggested

Drug sensitivity testing in vitro

The test was carried out as follows. A suspension of 100 000 to 250 000 trophozoites and cysts of acanthamoeba per ml was prepared in PBS. Washed live *Aerobacter aerogens* organisms grown in broth or on nutrient agar were suspended to an optical density of 6·0 at 650 nm in PBS. Drugs were prepared at a concentration 20 times that desired, also in PBS. 0·1 ml of amoebic and bacterial suspensions was added to 1·7 ml of PBS in sterile, screw-capped 10 ml test tubes, and 0·1 ml of drug solution was added. In control tubes 0·1 ml of PBS was added instead of drug solution. The test was carried out in duplicate. The tubes were incubated at 37°C for 48 hours. Five 0·02 ml samples were examined from mixed suspension from each tube to detect motile amoebae with typical acanthopodia. Where no apparently viable amoebae were found, the medium was centrifuged at 700 *g* for five minutes, and the sediment was inoculated on to non-nutrient agar plates coated with *A. aerogenes* and incubated further for 72 hours to detect any viable cysts or trophozoites

Each experiment therefore gave two results, a minimum inhibitory concentration (MIC) for inhibition of trophozoite growth (MIC.I) and MIC for killing of trophozoites and cysts (MIC.AmC). Tests were initially carried out on an isolate of acanthamoeba from a corneal ulcer which was undergoing treatment at Moorfields Eye Hospital.[1] Subsequent less extensive tests with the most effective drugs were carried out on new isolates as they were obtained.[10] Table 4 lists the results of the original wide-ranging drug screen.

Propamidine and dibromopropamidine

Propamidine and dibromopropamidine isethionate have long been available as ocular therapeutic substances as drops and ointment (Brolene, Otamidyl, May and Baker antiseptic cream) and have been used in the treatment of blepharitis and also superficial skin infection such as that complicating burns. The compounds show antibacterial and antifungal properties in addition to the amoebicidal effect reported here Dibromopropamidine isethionate is soluble 1 in 2 in water, and a 5% solution has pH 5·7. The commercially available preparation is a 0·15% cream (Brolene, May and Baker). It is reported to be active against pyogenic cocci, *Staphylococcus aureus*, Gram-negative organisms including *Escherichia coli*, *Proteus vulgaris*, and some strains of *Pseudomonas*. Propamidine isethionate is similar but less soluble in water, 1 in 5, and is commercially available as a 0·1% solution (Brolene eye drops). It shows a reduced spectrum of activity, being active against staphylococci and *Str. pyogenes* but inactive against *Pseudomonas*, *Proteus*, and *E. coli*.

The drops and ointment produced no serious adverse effects, but our experience of local irritation accords with the reported superficial necrosis of granulation tissue seen in some patients after topical application to wounds for more than 10 days. The initial treatment with Brolene was probably over-intensive, but subsequent therapy with the drops four times daily was well tolerated for two months, suggesting that any initial intensive treatment period should not be for more than one week and thereafter treatment four times daily or less should suffice. The optimum treatment regimen remains to be determined, but propamidine and dibromopropamidine seem to offer the first effective medical treatment of this challenging group of ocular infections.

Table 4 *Drug sensitivity of acanthamoba*

Drug type	*Chemical group*	*Name*	*I*	*AC*	*MIC I (μg/ml)*	*MIC AmC (μg/ml)*
Trypanocide anti-Leishmania	Diamidines	Berenil diaceturate	+	+	<5	<5
		Stilbamidine isethionate	+	+	<5	<5
		2OH stilbamidine isethionate	+	+	<5	<5
		Pentamidine isethionate	+	+	<5	<5
	Antimonial	Sodium stibogluconate	–	–	>156	>156
Antibiotic	Macrotetralide	Monensin sodium	–	–	>125	>125
	Macrolide	Venturicidin	+	+	2·5	156
	Polyene Macrolide	Candicidin	+	–	<25	>25
		Amphotericin B	–	–	>125	>125
		Azalomycin	+	+	9·8	9·8
	Polypeptide	Polymyxin B sulphate	+	+	39	313
		Gramicidin	+		313	
	Aminoglycoside	Paromomycin sulphate	+	+	9·8	9·8
		Neomycin sulphate	+	+	19·5	19·5
		Gentamicin sulphate	–		>156	
Fungicide		Miconazole	+	–	67·5	>250
		M & B 938	+	+	<5	<5
		Clotrimazole	–	–	>125	>125
	Bayer 1703	Clotrimazole analogue	+	–	<5	>156
		5-Fluorocytosine	+	–	156	>156
Antiviral		3-Fluorothymidine	–	–	>125	>125
Fungicide and antibacterial	8-Quinolinol	Steroxin	+	–	78	>156
		8-Hydroxyquinoline	+	+	9·8	78
Antianaerobe	5-Nitro imidazole	Metronidazole	–	–	>156	>156
Anthelmintic		Hetolin	+	–	39	>156
		Levamisole	+	–	<125	>125
		Diethylcarbamazine citrate	–	–	>156	>156
		Thiabendazole	–		>156	
Antiamoebic	Dichloroacetamide	Mebinol complex	+	+	55	438
Antimalarial Schizontocide		Mepacrine HCl	+	+	39	39
		Chloroquine diphosphate	–	–	>156	>156
PAB or folic analogues	Sulphonamide	Sulphamethoxazole	–	–	>156	>156
	Triazine	Trimethoprim lactate	–		>156	
Miscellaneous		Myxin	+	+	9·8	9·8
		Ziram	+	+	<5	9·8
		Fubendazole	+	+	39	156
		Carnidazole	–	–	>156	>156

I=inhibition of trophozoite growth AmC=amoebicidal (i.e., subculture negative) MIC=minimum inhibitory concentration
+=Drug effective –=No effect

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Bilateral recurrent orbital inflammation associated with retroperitoneal fibrosclerosis

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SUMMARY Orbital inflammation initially presented in a patient who five years later developed renal obstruction from retroperitoneal fibrosclerosis. Biopsy revealed infiltration of chronic lymphocytic cells in the orbit and dense fibrous connective tissue in the pelvis. Episodes of proptosis were controlled with systemic steroids and non-steroidal anti-inflammatory agents. The hydronephrosis was relieved by intraperitonisation of the ureters. Similarities to previously reported cases are discussed. This case shows the importance of searching for systemic disease in patients with orbital inflammatory disease and informing the patients of the possibility of future systemic manifestations of their disease.

Unilateral or bilateral orbital inflammation associated with varying degrees of proptosis, fibrosis, and limitation of ocular motility (orbital pseudotumour) has been observed to occur in individuals who also have systemic diseases such as sarcoidosis, Wegener's granulomatosis, histicytosis-X, thyroid disease, Waldenström's macroglobulinaemia and polyarteritis nodosa.[1 2] Comings and co-workers[3] were the first to report the association of orbital inflammation with retroperitoneal fibrosis, and, because they observed the condition in two brothers, they suggested the name 'familial multifocal fibrosclerosis.' We wish to report a non-familial case in which the initial episode of orbital inflammatory disease preceded by five years the development of obstructive ureteral-renal disease secondary to retroperitoneal fibrosis. This case illustrates the importance of searching for evidence of systemic disease in patients with orbital inflammatory disorders and of informing the patients of the potential for future systemic manifestations of their disease.

Case report

A 36-year-old white man presented on 26 January 1975 with sudden onset of proptosis, chemosis, and ophthalmoplegia of his left eye. These symptoms were preceded by a two-week history of a mild febrile illness and weakness. The patient had previously been in good health and gave no history of ingestion of medications such as methysergide. He had no history of chronic gastroenteritis. His three sisters and one brother were in good health. His mother had surgery at the age of 30 to remove fibrous tissue from her chest that obstructed her swallowing. No further symptoms developed, and she is well at age 68. At the time of his initial ocular examination the patient's uncorrected visual acuity was 20/25 in each eye. The pupils were equal and reactive. The conjunctiva of the left eye was hyperaemic and chemotic. The left globe and orbit were tender to palpation, and obvious left proptosis was present The left globe was depressed. There was initially limitation of upgaze only, but this progressed to total ophthalmoplegia within 24 hours.

On admission to hospital his laboratory tests were found to be normal, except for a raised Westergren sedimentation rate of 41 mm/h. Bilateral carotid arteriograms were normal. Orbital tomograms showed slight bony erosion of the left greater wing of the sphenoid.

On 4 February 1975 a Krönlein decompression and exploration of the left orbit was done. No localised mass was found. Three pieces of diffusely inflamed soft tissue and lacrimal gland were obtained. Histological examination (Fig. 1) revealed focal areas of chronic lymphocytic infiltration compatible with a diagnosis of lymphoid pseudotumour of the orbit. The tissue did not appear to be fibrotic.

80 mg of oral prednisone was started daily, and the

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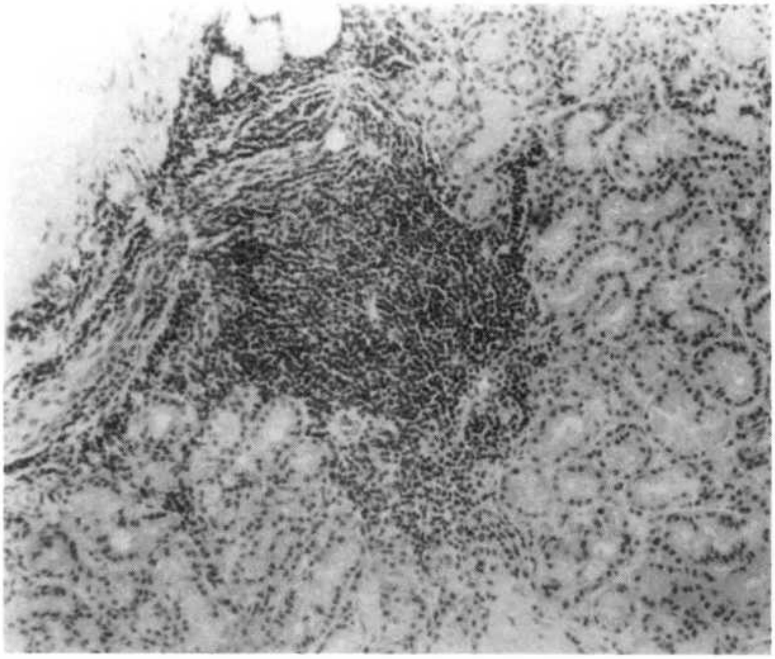

Fig. 1 *Biopsy of benign lacrimal gland with focal benign lymphocytic infiltrates. (H and E, ×300).*

patient was discharged from hospital on 7 February 1975. The oral prednisone was gruadually tapered to 25 mg every other day. On 28 February 1975 the patient developed pain and swelling about his right eye. No ophthalmoplegia was present. Repeat orbital tomograms were normal. Prednisone was increased to 80 mg daily, and as the right periocular pain and swelling subsided the prednisone was slowly tapered until it was discontinued in July 1975. He was seen intermittently for routine ocular examinations

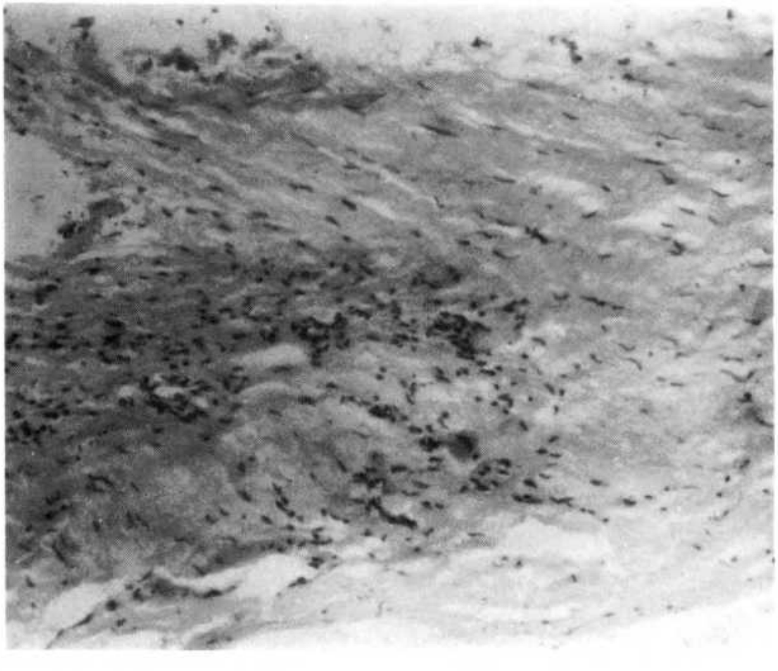

Fig. 2 *Biopsy of perirectal mass with benign fibroconnective tissue.*

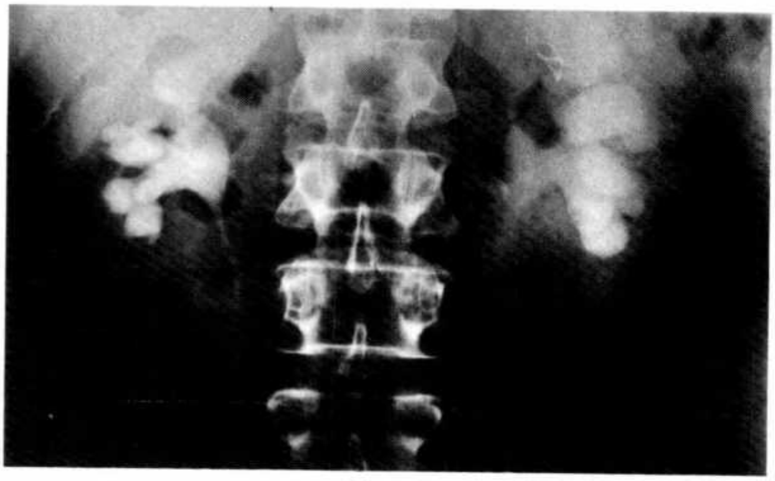

Fig. 3 *Intravenous pyelogram illustrating moderate hydronephrosis on the right and severe hydronephrosis on the left from bilateral ureteropelvic obstructions.*

after his discharge from the hospital. No proptosis or problems of extraocular motility were present during these examinations.

In July 1980 the patient was admitted to the hospital for investigation of a pelvic mass and haematuria. A pyelogram revealed obstruction of the right ureter at the pelvis, and the bladder appeared elevated and compressed. On 2 July 1980 cystoureteroscopy and a right pyeloureterogram were performed. Biopsy of a mass at 4 o'clock in the left sacrococcygeal wall was done through a proctoscope. The biopsy showed non-inflamed, benign, fibrous connective tissue (Fig. 2).

The patient was readmitted to hospital in May 1981 for investigation of bilateral progressive hydronephrosis and fever of unknown origin. During this spell in hospital he developed bilateral mild anterior uveitis, which responded to topical prednisone and mydriatic therapy. Right orbital congestion with 5 mm of proptosis and some limitation of extraocular motility also became apparent. Computerised tomography (CT) scans of the orbits confirmed the proptosis and demonstrated attenuation of the fat of the right orbit. There was slight enlargement of the extraocular muscles, but this was not thought to be characteristic of the myopathy accompanying thyroid disease.

On physical examination he was found to have an enlarged spleen and liver. However, CT scans of the abdomen and bipedal lymphangiograms were normal. An intravenous pyelogram now showed bilateral hydronephrosis (Fig. 3). Retrograde pyelograms showed an inflammatory process of the renal pelvis with obstuction at that level. The urine analysis was normal. The blood urea nitrogen (BUN) was 12 mg/dl (2·0 mmol/l) and serum creatinine was 1·4 mg/dl (124 µmol/l). Thyroid function tests showed a thyroxine radioimmunoassay of 6·8 µg/dl with thyroxine-binding globulin of 1·00 µg/dl. (SI conversion: µg-dl×10=µg/l.) Thyroglobulin antibodies were normal at less 1:10 and microsomal AB was normal at less than 1:100. The LATS-TSH was normal at 6µl/ml (6 ml/l).

On 26 May 1981 surgical lysis of retroperitoneal fibrosis with intaperitonisation of the ureters was carried out to relieve the bilateral hydronephrosis. The patient was found to have a 4–7 mm thick sheath-like fibrosis extending from just above the lower pole of each kidney to 2·5 cm below the iliac vessels. The fibrosis completely encased the ureters and extended over the great vessels but did not constrict them. The liver, spleen, and other abdominal organs were examined and found to be healthy and not involved in the fibrotic process. Biopsy from the retroperitoneal fibrotic-appearing tissue was found to be histologically consistent with the tissue changes observed in the 1980 biopsy (Fig. 4). He was treated with 50 mg of prednisone daily following his surgical exploration. This resulted in resolution of the proptosis and ophthalmoplegia. The steroid therapy was tapered and stopped in July 1981. He was subsequently treated with a non-steroidal anti-inflammatory agent (ibuprofen 1600 mg daily). This was discontinued in January 1983.

The patient remained asymptomatic until May 1983, when he again developed pain and swelling about his left eye. His left upper eyelid and superior orbit were red and tender, and there was limitation of upgaze. Mild anterior uveitis was also present in the left eye. The inflammation rapidly subsided on treatment with ibuprofen. His visual acuity remained 20/20 and the visual fields were unaffected. An intravenous pyelogram was normal, and no systemic symptoms developed. When last seen in August 1983

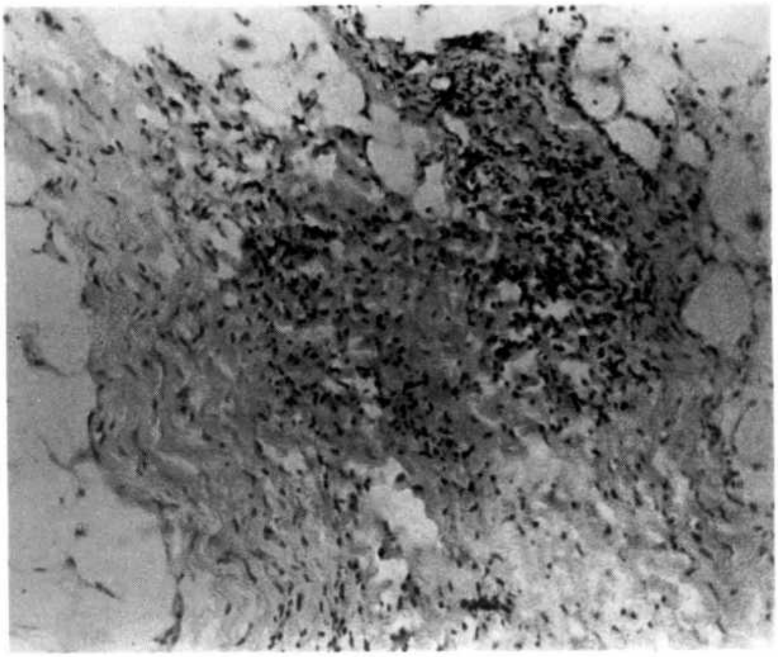

Fig. 4 *Retroperitoneal biopsy showing fibrous tissue with some areas of chronic inflammatory cell infiltration. (H and E, ×300).*

he was asymptomatic and was being treated with 1600 mg of ibuprofen daily.

Discussion

We are aware of three previously reported cases of orbital inflammation with proptosis (orbital pseudotumour) in association with retroperitoneal fibrosis and obstructive renal disease.[3,4] This entity was first described in 1967 by Comings and coworkers, who reported the ocular and abdominal findings in two brothers.[3] Their first patient, a 37-year-old man, initially presented with symptoms of recurrent episcleritis, which 10 years later recurred in association with proptosis and with gastrointestinal symptoms of nausea, vomiting, and lower abdnominal pains. A non-functioning kidney and hydronephrosis were found. A sheet-like fibrosis covering the ureters was noted on exploratory laparotomy. Biospy showed dense fibrous tissue infiltrated with leucocytes and plasma cells. The patient's 39-year-old brother had recurrent episodes of arthralgia of the hands as a child. By the age of 18 he had progressive dyspnoea on exertion. The trachea and vena cava were found to be encased in a fibrous mass during exploratory thoracotomy. At the age of 33 exophthalmos of his right eye developed. An orbital biopsy was not obtained in either patient.

Richards and coworkers[4] reported on a 66-year-old woman with a three-year history of declining health secondary to renal failure and a six-month history of painless proptosis of her right eye. Biopsy specimens of the orbit and of the abdomen were stated to be similar and to be composed of fibrous connective tissue interspersed with collections of acute and chronic inflammatory cells.

As we have noted in the introduction to this report, orbital inflammation and episcleritis associated with proptosis and limitation of ocular motility may occur in individuals with several forms of coexisting systemic inflammatory diseases. These may respond to treatment and resolve without residual fibrosis, but late scarring and limitation of eye movements often occur. Our patient has not shown clinical signs or laboratory findings consistent with any of these conditions. He has not developed postinflammatory orbital fibrosis, and the orbital biopsy showed no evidence of necrosis or of scarring. Nevertheless we assume that a relationship exists between his recurrent ocular inflammatory episodes and his retroperitoneal fibrotic lesions.

The pathogenesis of multifocal fibrosclerosis is unknown. It has been proposed that the retroperitoneal fibrotic component represents a localised secondary response to gastrointestinal inflammation.[5] A similar retroperitoneal process may be initiated by the ingestion of methysergide.[6] Retroperitoneal fibrosis causing extrinsic ureteral obstruction was first described by Albarran.[7] The fibrous process may exist without creating ureteral obstruction, but the ureter is quite vulnerable to compression and distortion by the fibrosis and is therefore the structure most frequently affected. The inferior vena cava and aorta may also be involved.[8]

In our case the retroperitoneal mass was described by the surgeon as a fibrotic wall, and biopsy specimens showed only thickened fibrotic tissue. Specimens with these characteristics may initially be regarded as being inadequate, especially in cases where a malignancy is suspected because of the obstructive nature of the disease. Care must be taken to make certain that adequate specimens are obtained from different sites and that the process is indeed benign, since a similar fibrotic process may be seen with carcinoma of the sigmoid, carcinoid tumours, reticulum cell sarcoma, and Hodgkin's disease.[3] Once the benign nature of the obstructive disease is established, intraperitoneal transplantations of the ureters to relieve the urinary obstruction has been recommended.[5] This procedure was successful in our patient, and he is now asymptomatic. The patient's mother had a past history of surgery for oesophageal obstruction; this suggests a possible familial incidence. However, the histological diagnosis of her chest lesion is unknown; there has been no recurrence of her disease, and she has not shown ocular or other abnormalities of the type associated with multifocal fibrosclerosis.

It appears that the use of non-steroidal anti-inflammatory agents has been beneficial in suppressing recurrence of this patient's orbital inflammation. He has had only one recurrence since his hospitalisation, but this occurred while he was off his medication. Because of the short follow-up interval in this case the long-term benefit of this form of therapy is uncertain.

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Effect of praziquantel on intraocular cysticercosis: a case report

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SUMMARY A patient with intravitreous cysticercosis was treated with the new anthelminthic drug, praziquantel. A transient toxic effect on the cysticerus was observed, but the drug was unable to kill the parasite.

Although a pars plana vitrectomy is the treatment of choice of intravitreous cysticercosis,[1,2] this sophisticated method is not readily available in most developing countries where the disease is most prevalent. So a medical treatment would be most welcome. Recently praziquantel,[3] a heterocyclic pyrazinoisoquinoline derivative, has been shown to be highly effective against a broad range of helminths, including the four human schistosoma species, most of the other flukes, the tapeworms as well as *Cysticercus cellulosae*, the larval stage of *Taenia solium*, the causal agent of cysticercosis. The drug is rapidly absorbed on administration and reaches peak serum levels about 1 μg/ml one to two hours after an oral dose of 50 mg/kg in adults. Concentrations of 14 to 20% of the amount of free plus protein-bound praziquantel in the plasma are found in the cerebrospinal fluid. After preliminary good results obtained in the treatment of porcine cysticercosis[4] praziquantel was used in a few cases of human neurocysticercosis[5,6] and found to be highly active. The efficacy of the drug was further substantiated by the results of several large clinical trials.[7-9] In a review of 172 patients with neurocysticercosis treated with praziquantel 87·2% of them were reported to have had either an excellent, a good, or a satisfactory response to the drug.[4] We here describe the effect of praziquantel in a case of intraocular cysticercosis.

Case report

A 45-year-old Rwandese male presented with a slightly red, painful right eye and complained of progressive visual loss for the previous six months. The visual acuities were weak light perception in the nasal field right and 6/6 left. He had a torpid right anterior uveitis with no flare but 1+ cells; posterior synechiae were present along the inferior half of the pupil and precluded a good view of the fundus. Indirect ophthalmoscopy through the hazy vitreous revealed an actively moving cysticercus larva with the scolex clearly visible and attached to the retina by a small stalk (Fig. 1). The left eye was entirely normal. Physical examination revealed some cutaneous nodules but was otherwise normal. Histological examination of an excised nodule confirmed the suspicion of cutaneous cysticercosis. Routine laboratory investigations, including full blood count, erythrocyte sedimentation rate, liver tests, urine and cerebrospinal fluid gave normal results. Since vitrectomy equipment was not available, we decided to try medical treatment with praziquantel. The patient took a daily dose of praziquantel 50 mg/kg body weight for two weeks, along with 50 mg prednisone to suppress the inflammatory reaction expected to occur in the eye and in other organs as a result of the destruction of parasites.[10,11] We performed indirect ophthalmoscopy twice daily to assess the effect of the drug on the motility and the morphology of the cysticercus.

During the first three days of treatment the parasite gradually shrank in size, the surface of the wall of cyst became slightly rough and irregular, and the scolex appeared swollen (Fig. 2). Although the cysticercus appeared immobile during direct ophthalmoscopic observation from the third day on, the fact that the scolex was seen in different positions at different times of day clearly indicated that the larva was alive and continued to move in slow motion

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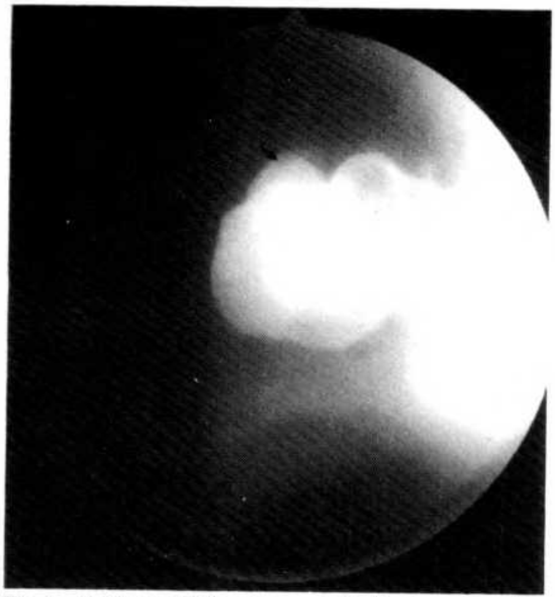

Fig. 1 *Cysticercus before treatment. Scolex (arrow) partly hidden.*

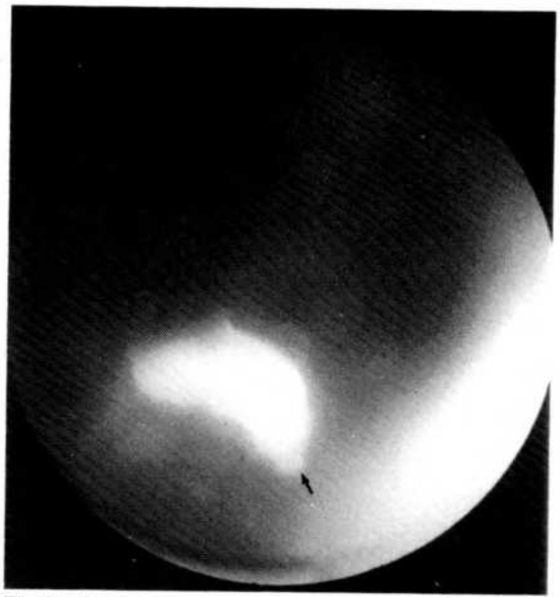

Fig. 2 *Cysticercus after five days of treatment. Scolex (arrow) points down.*

(Fig. 3). This situation remained essentially unchanged during treatment. Two days after the drug was stopped, the cysticercus seemed to have unfolded and to have regained its initial motility and morphology (Fig. 4).

During the first three days of treatment the patient complained of diffuse headache, which aroused the suspicion of central nervous system involvement. He had no history of seizures, and a clinical neurological examination gave normal results. No other secondary effects could be attributed to praziquantel in our patient. Blood count, urine analysis, and liver function tests were unchanged from before treatment.

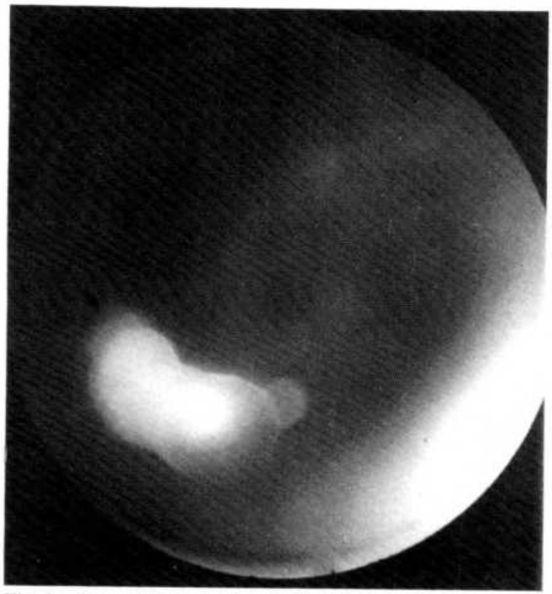

Fig. 3 *Same day as Fig. 2, some hours later. Scolex (arrow) now points up.*

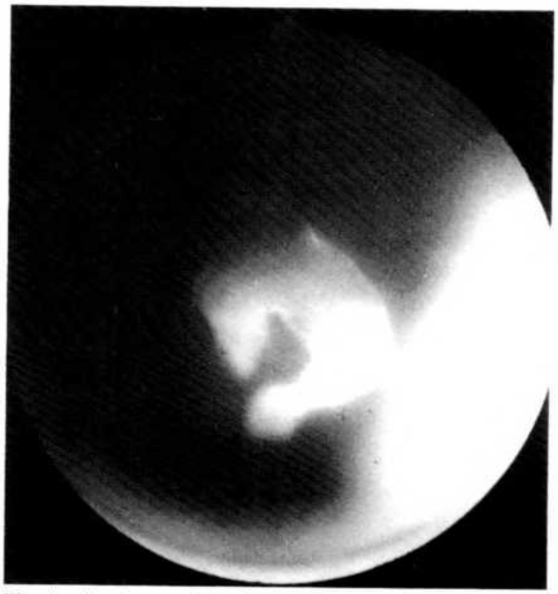

Fig. 4 *Cysticercus three days after the end of treatment.*

Discussion

Our observation is in agreement with the findings of others[8-12]: praziquantel exerts a toxic but reversible effect on the intraocular cysticercus. The fact that the drug is unable to kill the parasite is probably due to insufficient concentration at that site. In the treatment of neurocysticercosis with praziquantel it has been emphasised that drug levels in blood are different from levels in ventricular or subarachnoid cerebrospinal fluid and that the expected results would depend on parenchymal, ventricular, or subarachnoid localisation of parasites.[9] It is easy to understand that the localisation of an intravitreal cysticercus makes it a poor target for systemic treatment. There are two possible ways for praziquantel to reach an intravitreous cyst: first through the vitreous surrounding it, and secondly through the small stalk between the retina and the cyst. Most drugs penetrate poorly in the avascular vitreous, and, since praziquantel was unable to kill the parasites in two cases of subretinal cysticercosis,[12] the amount of drug passing from the retina to the cyst is unlikely to be sufficient.

It therefore appears that systemic medical treatment with praziquantel is not a valid alternative to vitrectomy in cases of intraocular cysticercosis. As the sophisticated equipment for performing this surgery is not available in most developing countries, it would be worthwhile determining the retinal toxicity of praziquantel in order to consider the possibility of giving it by intravitreous injection. The association of systemic and local treatment with praziquantel and steroids would provide the ophthalmologist in the third world with a weapon against a disease that now often ends in enucleation of a blind, painful, and unsightly eye.

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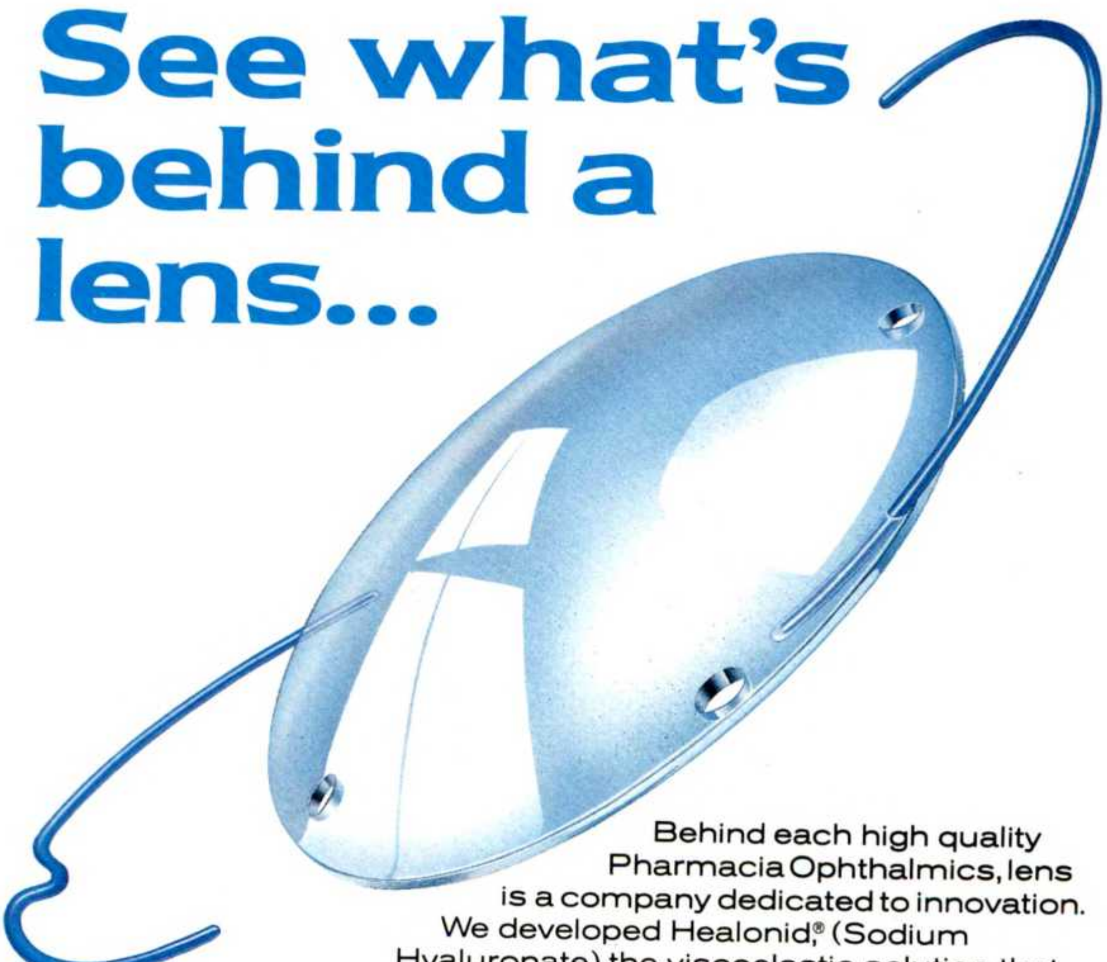

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British Journal of Ophthalmology, 1985, **69**, 791–794

Acquired Brown's syndrome: an unusual cause

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SUMMARY A 62-year-old man with acquired Brown's syndrome is presented. This was due to an orbital metastatic deposit, a cause not previously reported. Other causes of this disorder and its treatment are discussed.

Inability to elevate the adducted eye above the horizontal suggests an inferior oblique weakness, but such a paresis is rare. The more common cause of this restricted movement is an abnormality of the superior oblique tendon, its sheath, or the trochlea, preventing free passage of the tendon through the trochlea during inferior oblique action. The abnormality was originally described by Brown[1] and is known as the superior oblique tendon sheath syndrome or Brown's syndrome.

Brown originally postulated that the cause of the motility defect was a short anterior tendon sheath on the superior oblique tendon, possibly secondary to a congenital inferior oblique weakness. However, electromyographic studies have shown that inferior oblique function is normal in the syndrome.[2]

In 1973 Brown[3] redefined the syndrome, describing two main groups: *true*, which was congenital, permanent, and due to a congenital shortening of the anterior tendon sheath of the superior oblique; and *simulated*, where the defect could be either permanent or intermittent, was acquired, and had various aetiologies. Brown included congenital cases in the simulated group if a cause other than a shortened anterior tendon sheath was proposed. As this aetiology is speculative, this is likely to cause confusion.

Brown's hypothesis is disputed by Parks and M Brown,[4] who think that an abnormal tendon, lacking the normal elasticity, would better explain the clinical findings.

An abnormal insertion of the superior oblique tendon has been described[5] in congenital cases. The patients may not present until late childhood, and this may imply a progression of the disorder An abnormal relationship between tendon, sheath, and trochlea secondary to an abnormal insertion has been postulated as a cause of 'wear and tear' and a secondary tendon swelling.[6]

The mechanism of the acquired forms is either a nodule or swelling in the tendon behind the trochlea or adhesions between the sheath and tendon in its anterior parts. This would not interfere with movement of the tendon through the trochlea when the muscle is actively contracting but would prevent movement in the opposite direction.

The aetiology of the acquired form falls into two main categories: inflammatory and traumatic. The inflammatory cases can be due to local inflammation in the orbit—for example, contiguous infection of sinus or globe[4 7 8]—or part of more generalised inflammatory diseases such as rheumatoid arthritis and a tenosynovitis (as occurs in trigger-finger).[9] Direct trauma to the region of the trochlea may result in the syndrome.[10 11] Two cases have been described following windscreen glass injuries These initially presented as superior oblique weakness, but the motility disorder changed spontaneously to typical Brown's syndrome about one month after injury.[12] It is also seen after superior oblique tucking.[13] A similar appearance is seen after some orbital floor fractures,[14] although presumably the mechanism is different.

Both types may be intermittent, when the 'click' phenomenon may be present.[6] An audible or palpable 'snap' is noted by patient or examiner during attempted upgaze. This phenomenon is characterised by sudden restoration of full elevation following sustained effort[15] or pressure over the trochlea.[16 17] In congenital cases the click phenomenon is regarded as a stage in the resolution of the condition, the mechanisms postulated being either enlargement of the trochlea with growth, or 'wearing down' of the swelling with time.[18]

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We present here the case of a man with an unusual cause for a typical acquired Brown's syndrome.

Case report

A 62-year-old man was admitted to hospital in June 1983 with a four-month history of double vision. He had first noticed it while shaving and only on looking up into the mirror. For the preceding three months he had suffered bifrontal headaches. He had smoked 60 cigarettes a day until three years previously but had no other relevant past medical history. There was no history of ocular disease.

On examination the visual acuity was 6/5 unaided bilaterally. The visual fields, colour vision and pupil reactions were normal. The anterior segments and fundi were normal.

There was no ocular deviation in the primary position, and binocular single vision was present. There was a downdrift of the left eye on right gaze. Elevation of the left eye was almost totally restricted in adduction and near normal in abduction (Figs. 1A–I). When the patient looked up to the right, a cover test of the right eye produced no movement of the left, and a forced duction test was positive; both findings confirmed a mechanical restriction of the eye.

The Hess chart was characteristic (Fig. 2). Overaction of the contralateral superior rectus (i.e., yoke muscle of the inferior oblique) was seen, whereas the other muscle sequelae of a true inferior oblique weakness, such as ipsilateral superior oblique overaction or contralateral inferior rectus underaction, were not present. There was no proptosis or ptosis, but the medial end of the lid crease was indistinct, though no mass was palpable. There was no tenderness, and pressure over the region did not alter the motility defect. General medical and neurological examinations were otherwise normal. Apart from a moderately raised serum alkaline phosphatase, routine haematological, biochemical, and immunological tests were negative.

Skull and orbital x-rays were normal, but a chest x-ray showed a rounded opacity in the lingula. Needle biopsy showed this lesion to be an undifferentiated carcinoma. He was subsequently found to have a carcinoma of the prostate. Computerised tomographic scan of the left orbit showed a mass in the region of the superior oblique muscle (Figs. 3A, B). There was no bony erosion around the mass. This

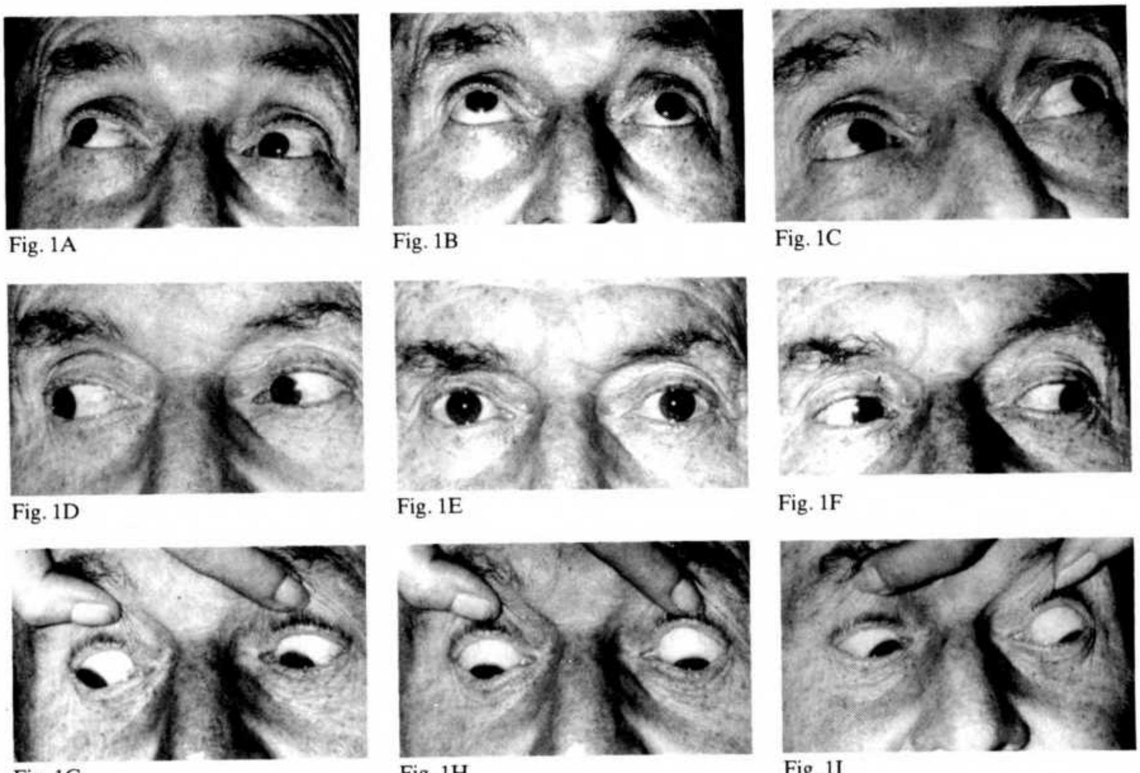
Fig. 1A Fig. 1B Fig. 1C

Fig. 1D Fig. 1E Fig. 1F

Fig. 1G Fig. 1H Fig. 1I

Fig. 1A–I *Positions of gaze. Note restricted elevation of left eye in right gaze.*

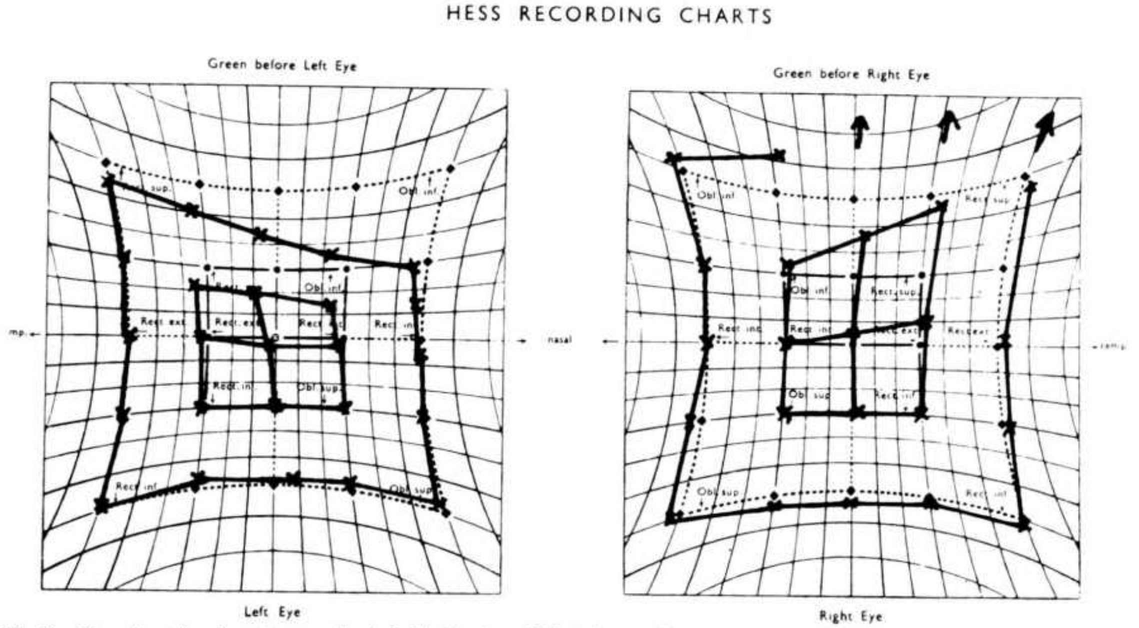

Fig. 2 *Hess chart showing abnormality in field of action of left inferior oblique and right superior rectus only. This implies a mechanical restriction in the field of action of the left inferior oblique.*

finding, together with early muscle involvement, strongly suggested a metastatic deposit.

Radiotherapy to the orbit was tried, but its effects on motility could not be accurately assessed because the patient developed cerebral metastases and deteriorated rapidly. He died shortly afterwards. Consent for necropsy was not obtained.

Discussion

This case fulfils all the criteria of acquired Brown's syndrome and illustrates several typical features. The lack of movement of the left eye on covering the right in dextro elevation suggests a mechanical restriction rather than a nerve palsy. This can be confirmed by

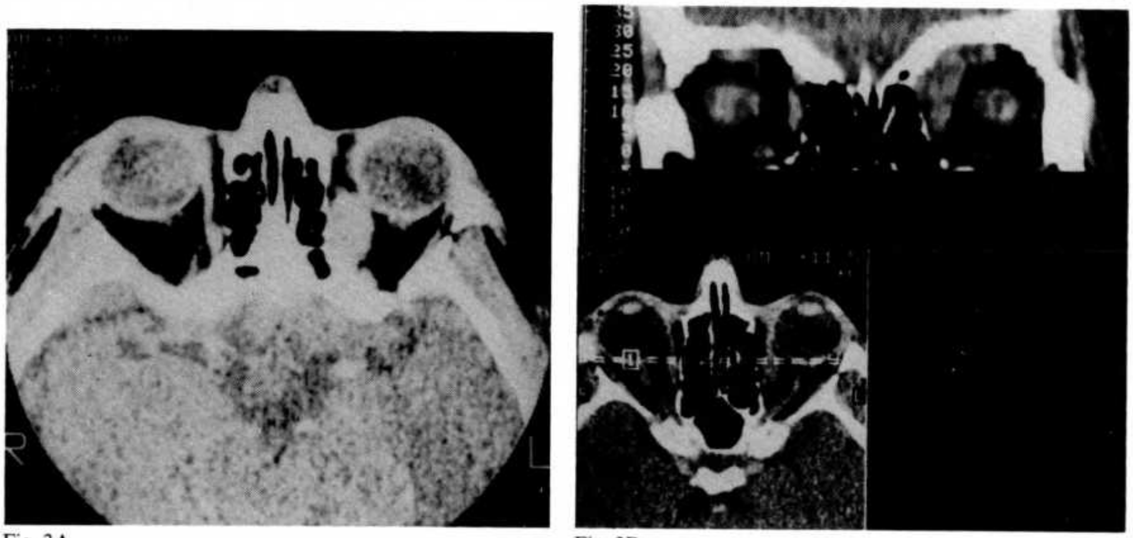

Fig. 3A

Fig. 3B

Fig. 3 (A) *CT scan of orbits, with* (B) *coronal reconstruction, showing mass in the region of the left superior oblique muscle.*

tonometry (the intraocular pressure will increase in upgaze if the eye is mechanically restricted) and by forced duction testing. The Hess chart confirms the lack of left superior oblique overaction and right inferior rectus underaction, suggesting that the motility disorder is restricted to certain gaze positions.

The mass demonstrated by CT scan would account for the defect. It would prevent free running of the anterior tendon forwards through the trochlea during elevation, and thus restrict this duction, without interfering with superior oblique action. The normal superior oblique function suggests that inflammatory adhesion round the mass was not a significant factor in the mechanism of the restriction of movement.

If inflammatory adhesion had been thought to be a factor, peritrochlear steroid injections would have been the first line of treatment, as benefit from such management has been recorded.[19 20] The results of surgery in both congenital and acquired forms of the syndrome are disappointing,[21 22] so it was not considered because of the patient's poor general prognosis. Radiotherapy seemed logical and was tried. The deterioration in the patient's condition prevented any accurate assessment of its effects.

This case illustrates the need for a thorough systemic examination in patients who present with acquired Brown's syndrome. Associated systemic disease may be uncovered, and its nature may give a clue as to the pathophysiology of the syndrome and thus indicate which treatment may help.

We thank Professor W I Macdonald for permission to report this case under his care, Mr D Taylor for his helpful advice, Mr C Clements for help with the illustrations, and Mrs K Kyle for secretarial assistance

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British Journal of Ophthalmology, 1985, 69, 795

Correspondence

Anterior chamber angle in the exfoliation syndrome

SIR, Wishart, Spaeth, and Bryzees[1] report an incidence of 14% of angle closure glaucoma among 76 patients with the exfoliation syndrome. They believe that earlier reports indicating no association between a narrow anterior chamber and the exfoliation syndrome represent incomplete observation.

I reported an association between angle closure and exfoliation syndrome in 1979.[2] In 1981[3] I gave a full description of 13 patients with angle-closure glaucoma out of a total of 107 with glaucoma and exfoliation syndrome, 12%, a percentage similar to that of Wishart *et al*. I suggested a mechanism of 'iridocapsular' block and presented three patients cured by peripheral iridectomy, first described by Herbst,[4] and one by mydriasis. I concluded that such cases would be discovered by better observation and therefore correct management would follow.

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SIR, We thank Dr Bartholomew for his interest in our article[1] and for drawing our attention to two of his earlier publications.[2,3]

In the first of these two papers Dr Bartholomew reports an average fall in intraocular pressure following cataract extraction in seven patients with exfoliation syndrome and glaucoma. He suggests relief of iridocapsular block as a possible mechanism responsible for this fall in pressure. However, as no record of gonioscopic findings appears, this suggested mechanism remains conjecture and we fail to see the relevance of this to our results.

In the other paper to which he refers Dr Bartholomew describes 16 cases of acute glaucoma, 13 of which were ascribed to acute angle closure. The lack of details of material and method, the absence of information about the angle appearance in all patients included in this study, and the lack of explanation as to why peripheral iridectomy was such a rarely used treatment for acute angle closure all make it difficult for the reader to draw any conclusions from this study about the anterior chamber angle in the exfoliation syndrome.

Dr Bartholomew's two papers are in support of the theory of iridocapsular block as a mechanism of glaucoma in the exfoliation syndrome. Our study was of the gonioscopic findings in patients with exfoliation syndrome and does not speculate on the possible dynamics involved in the production of angle-closure glaucoma.

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Angle closure following neodymium—YAG (Nd-YAG) laser capsulotomy in the aphakic eye

SIR, The Nd-YAG laser has gained popularity as a 'non-invasive' means of dividing intraocular membranes. Initial reports suggested that complications were rare.[1] Recently intraocular lens damage,[2,3] rupture of the anterior hyaloid face,[2] corneal endothelial damage,[3] and significant pressure rise[2,3,4] have all been reported to follow Nd-YAG posterior capsulotomy in the aphakic eye. We wish to report a case in which Nd-YAG capsulotomy was followed by acute angle-closure glaucoma.

Case report

A 49-year-old woman underwent a planned, uncomplicated, left extracapsular cataract extraction for a unilateral lens opacity. A peripheral iridectomy was not performed. Postoperatively she received topical atropine and steroids for four weeks. She initially achieved a visual acuity of 6/9 with a contact lens, but one year later her corrected visual acuity fell to 6/60 owing to thickening of the posterior capsule. She declined further surgery. Three years after her operation she elected to have a Nd-YAG capsulotomy. No preoperative medication was administered. A Q-switched Nd-YAG laser (Cooper Vision) was employed in its burst mode, and a successful capsulotomy achieved with three bursts of four shots with a total energy delivery of 36 mJ. One drop of atropine 1% was instilled and she was allowed home.

Forty-eight hours later the patient presented with a 24-hour history of left painful red eye. Corneal oedema was present with an intraocular pressure (IOP) of 50 mmHg and minimal activity in the anterior chamber. The pupil was dilated, the anterior chamber was deep centrally but shallow peripherally, and the angle closed all round

There was no iris bombé and no pupil block Initial treatment comprised topical steroid and timolol with oral acetazolamide This was unsuccessful The addition of 2% pilocarpine 12 hours later successfully controlled the intraocular pressure All treatment was stopped the following day, and the intraocular pressures remained at 14 mmHg. The drainage angle was wide open all round, and a mydriatic test performed two weeks later was negative Her visual acuity improved to 6/9 with her contact lens and no visual field loss was detected.

To our knowledge angle closure, without pupillary block, following Nd-YAG laser capsulotomy has not previously been reported. A rise in intraocular pressure, which may exceed 50 mmHg, is a well documented complication of this procedure, but timolol and/or acetazolamide have hitherto been used successfully in treatment Explanations which have been given for the pressure rise include diminished outflow facility resulting from deposition of debris in the trabecular meshwork[4]; neurovascular mechanisms[7], trabeculitis as a result of the radiating shock wave[6]; and pupillary block.[1] In this case it was initially considered that inflammatory swelling of the ciliary body secondary to the pressure wave was the most likely pathogenetic mechanism of angle closure, which provided the rationale for the use of steroid However, pilocarpine successfully reduced the intraocular pressure, implicating such mechanisms as angle crowding due to swelling of the iris root or ciliary body.

This report serves to illustrate that careful observation and follow-up is warranted for all patients undergoing Nd-YAG laser treatment to the eye, as hitherto unreported complications are likely to be observed when this novel treatment becomes more widely used

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Book reviews

Chirurgie des Strabismes. By P V BÉRARD, M A QUÉRÉ, A ROTH, A SPEILMANN, M WOILLEZ. Pp. 470. 520F. Masson: Paris. 1984.

This large (470 page) book is a collaboration by five members of the Société Française d'Ophtalmologie all of whom are well known in the field of ocular motility and strabismus. As the title suggests, this is a large and compendious manual of surgical techniques and methods in strabismus and related conditions such as nystagmus. I could find no notable omissions, and in particular the diagrams and bibliography are excellent. The only major fault is one common to all books of this kind, that it is difficult for the unknowledgeable reader to get good advice on what procedure to choose in any particular clinical situation. Perhaps a little more attention could have been paid to the timing of surgery, especially in congenital esotropia, but nevertheless all the relevant authors are quoted.

This book deserves a good, sympathetic translation into English, as it represents the most complete listing of techniques in strabismus surgery currently available.

J P LEE

Hyaline Membrane Disease: Pathogenesis and Pathophysiology. Edited by LEO STERN. Pp. 297. £30·50. Grune and Stratton: London. 1984.

This monograph, which is of considerable value to the paediatrician and neonatologist, must be of limited interest to an ophthalmological readership It provides a detailed up-to-date account of the pathogenesis, clinical features, and complications of this condition, with many eminent contributors The book is subtitled pathogenesis and pathophysiology, and it is in this area that it makes its greatest contribution. The chapters on clinical management and follow-up are less comprehensive.

Although there is a section on pulmonary oxygen toxicity, there is scant mention of retrolental fibroplasia, which fails to feature at all in the index. The chapter on follow-up does mention that up to 32% of survivors of mechnically ventilated premature infants with birth weights of less than 1250 g may develop this condition, which remains a major hazard in the management of premature infants with hyaline membrane disease and other oxygen dependent conditions. It deserves greater emphasis in this text with at least a reference to its sister volume in this series of Monographs in Neonatology —Retrolental Fibroplasia, a Modern Parable by W A Silverman.

D J MATTHEW

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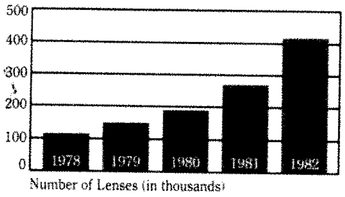

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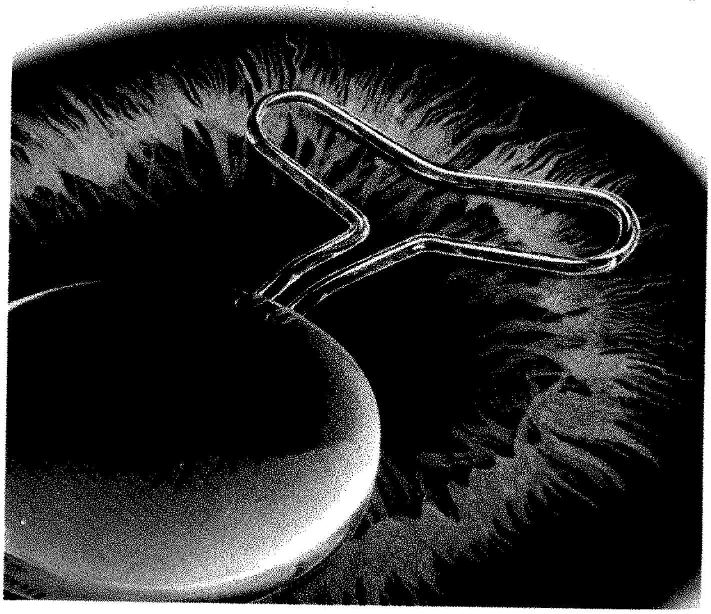

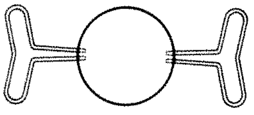

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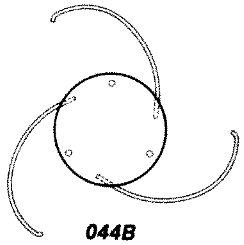

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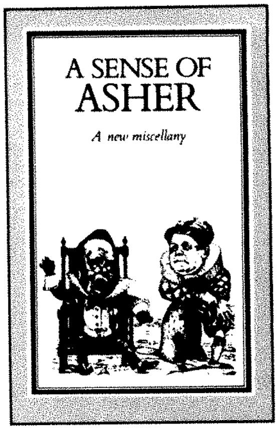

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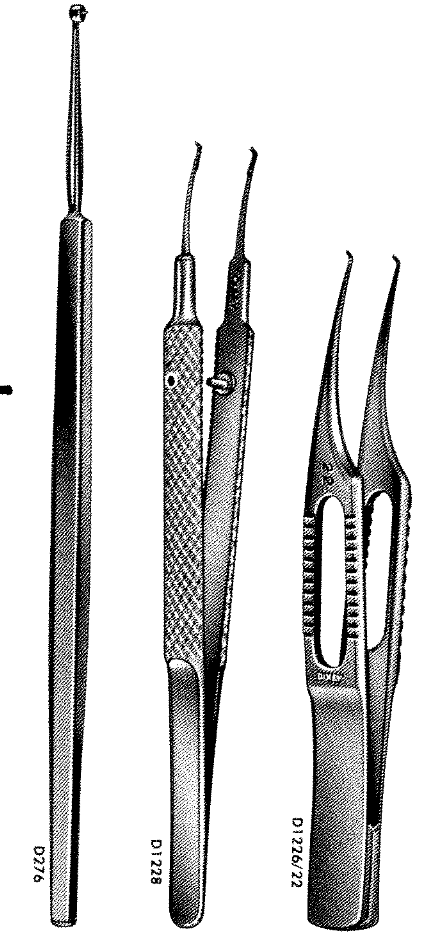

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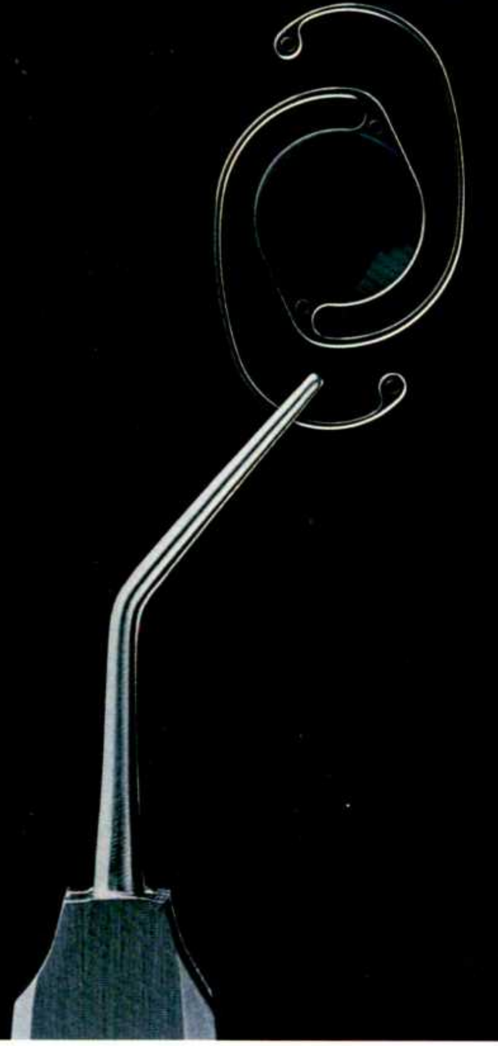

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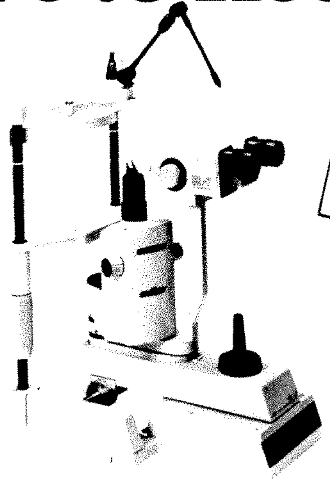

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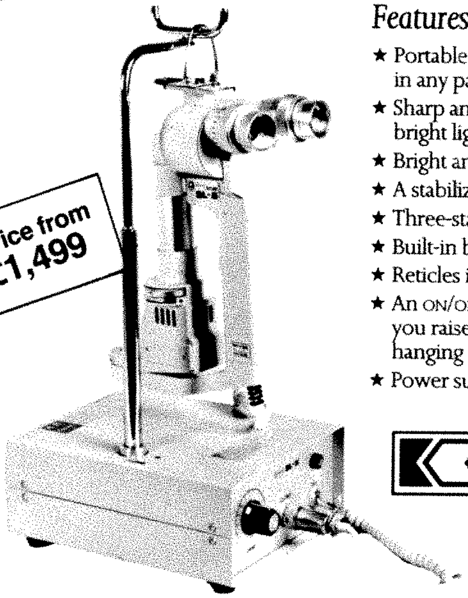

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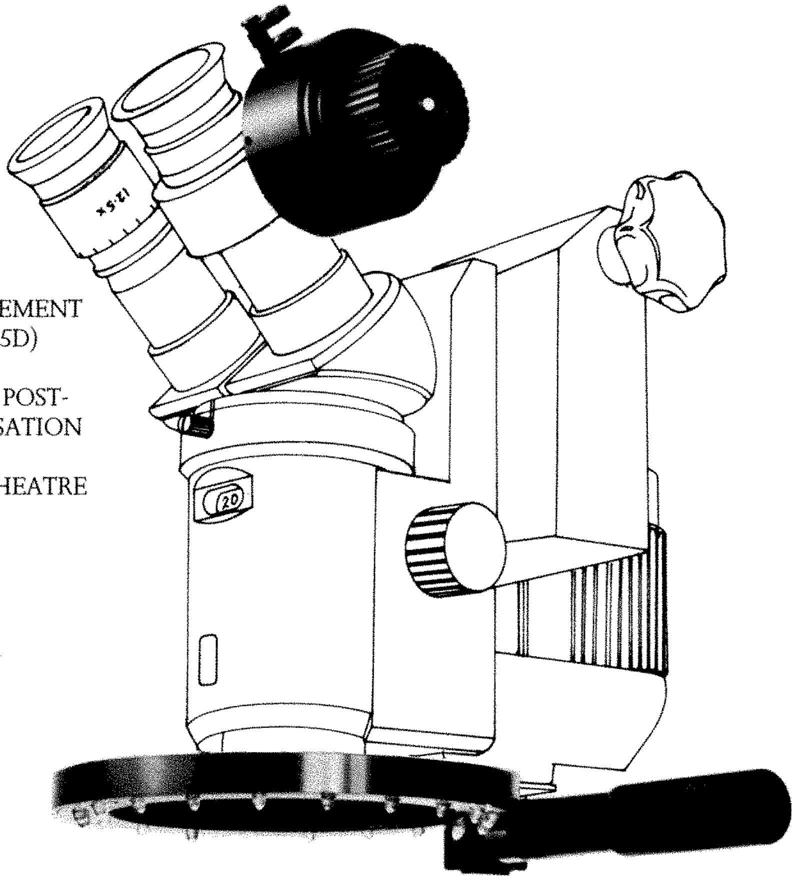

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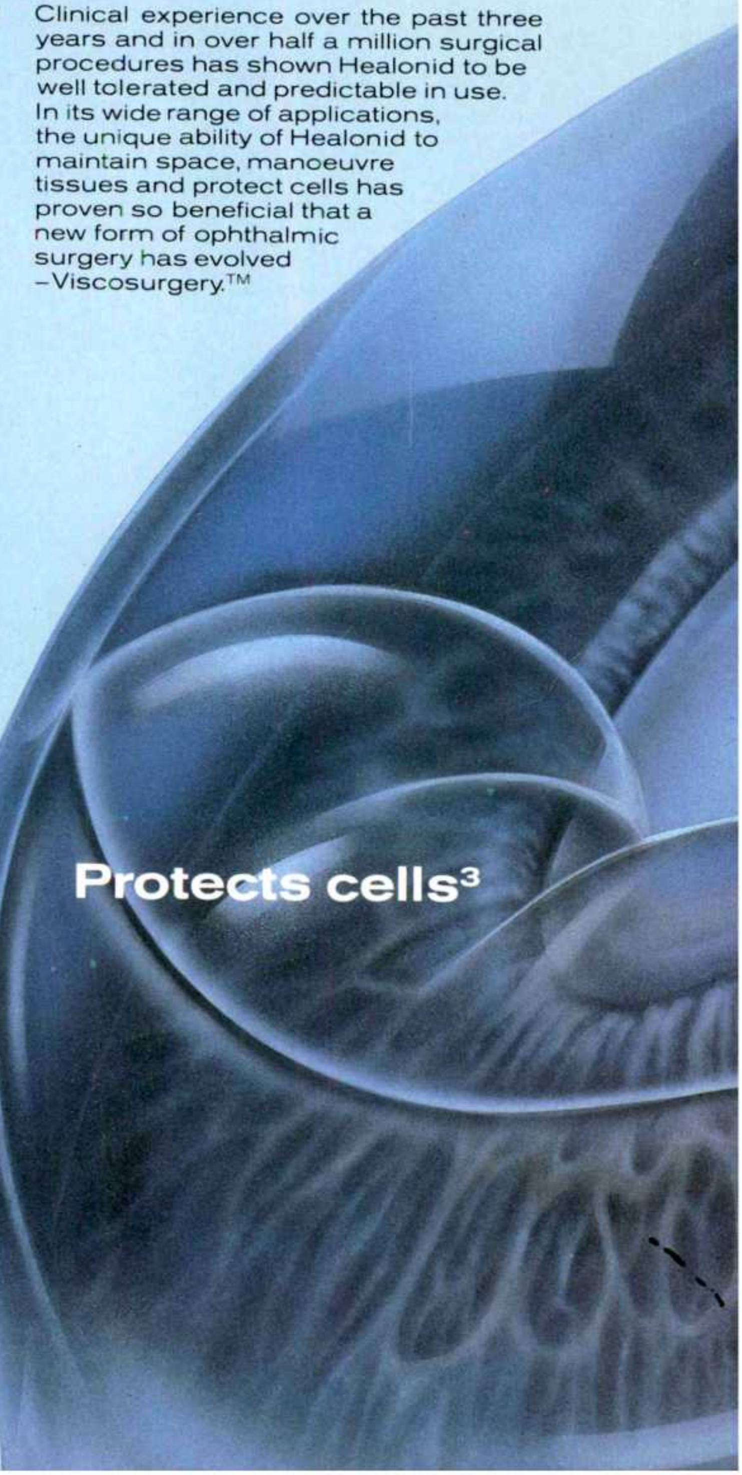

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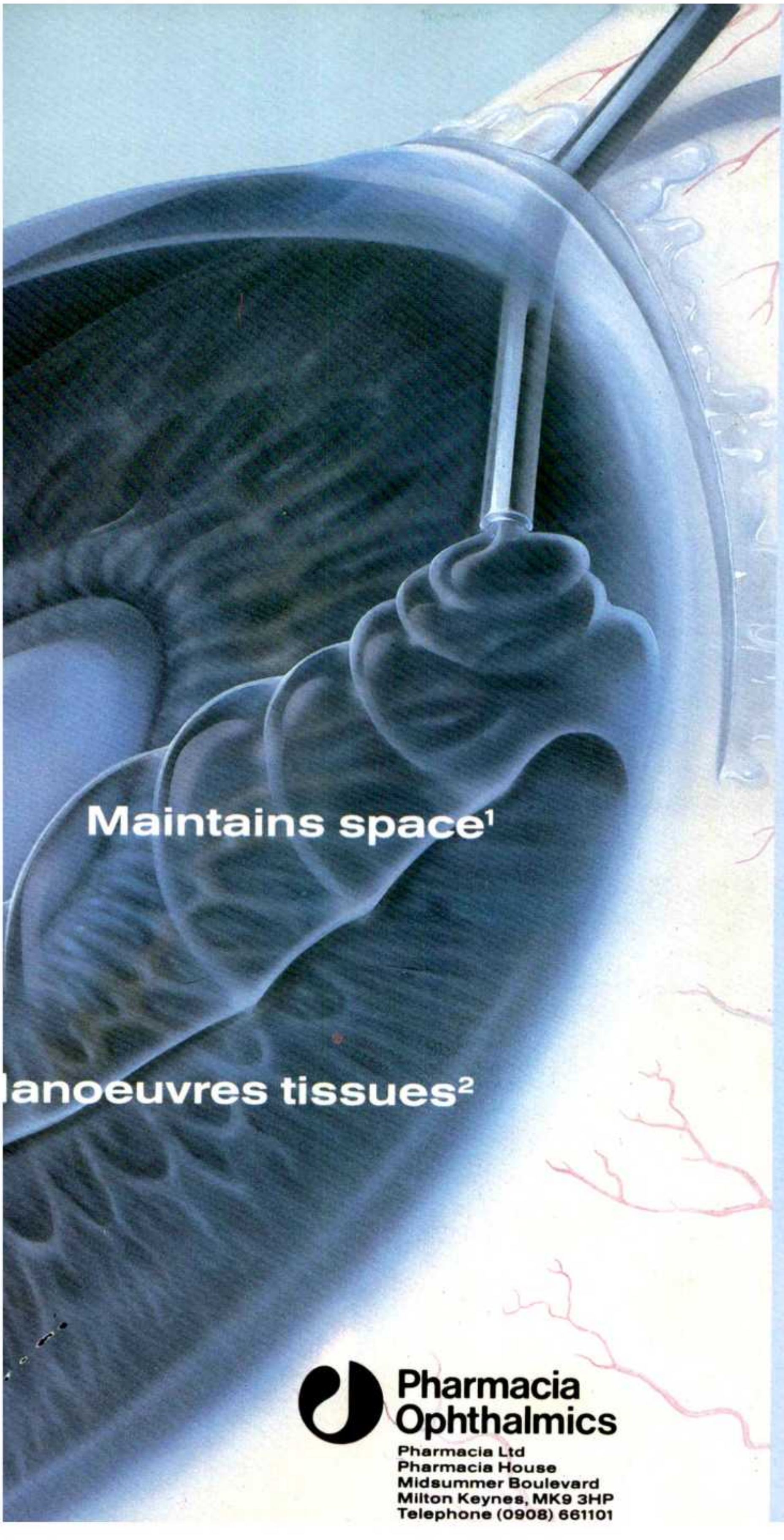

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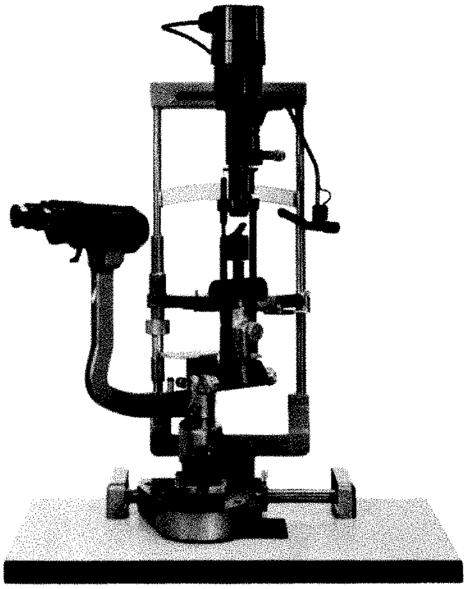

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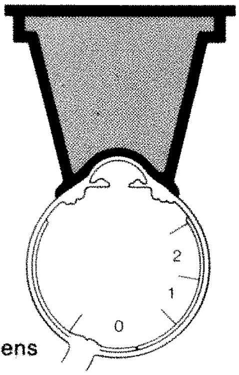

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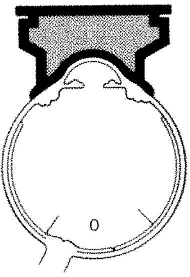

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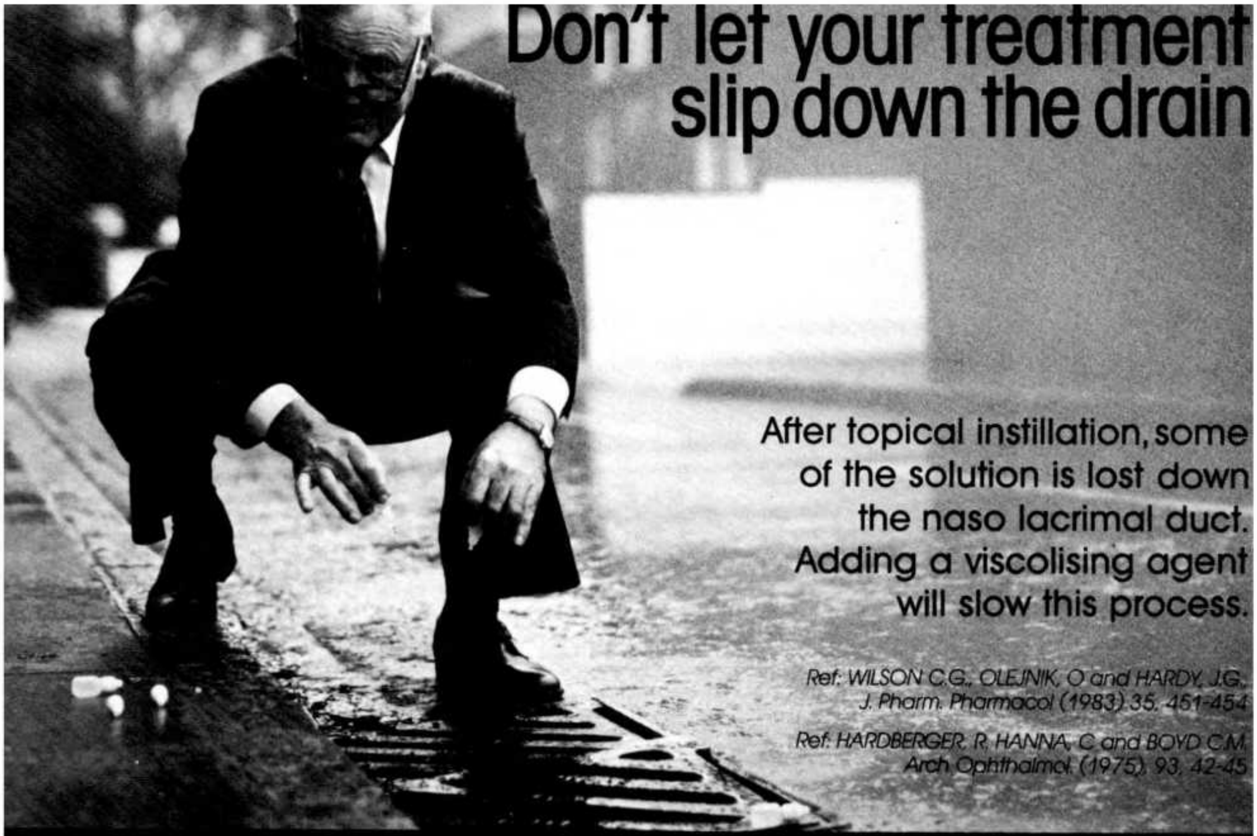

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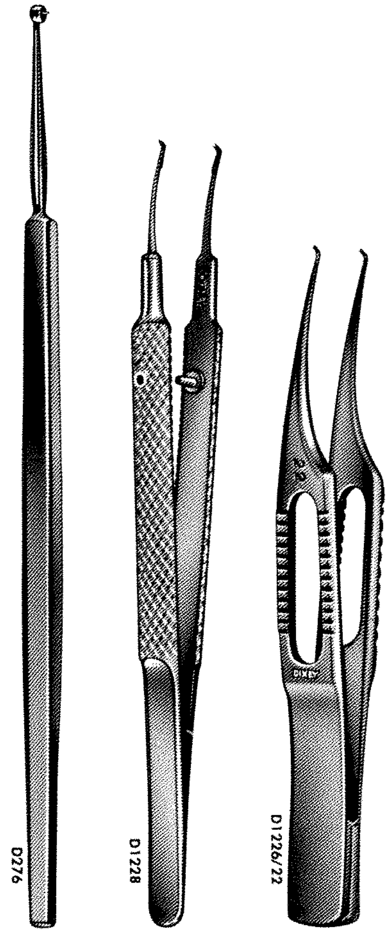

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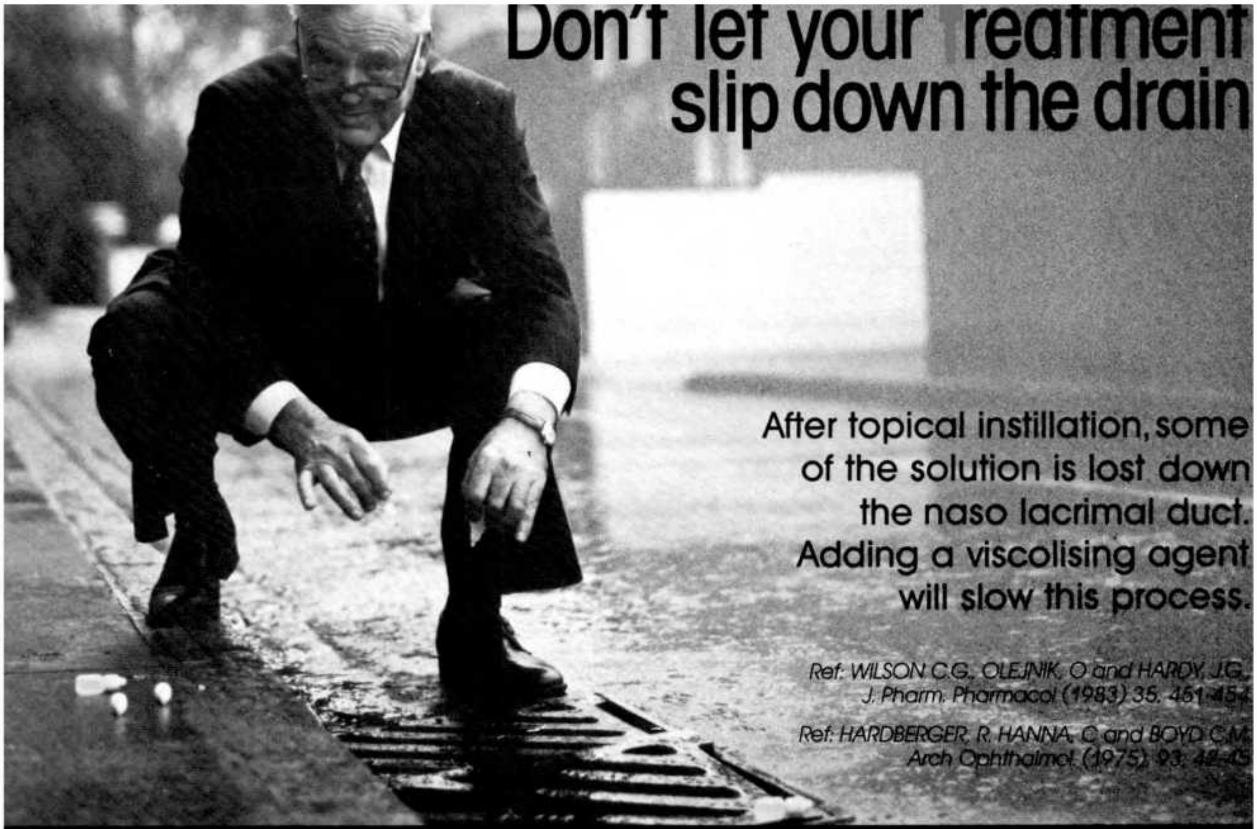

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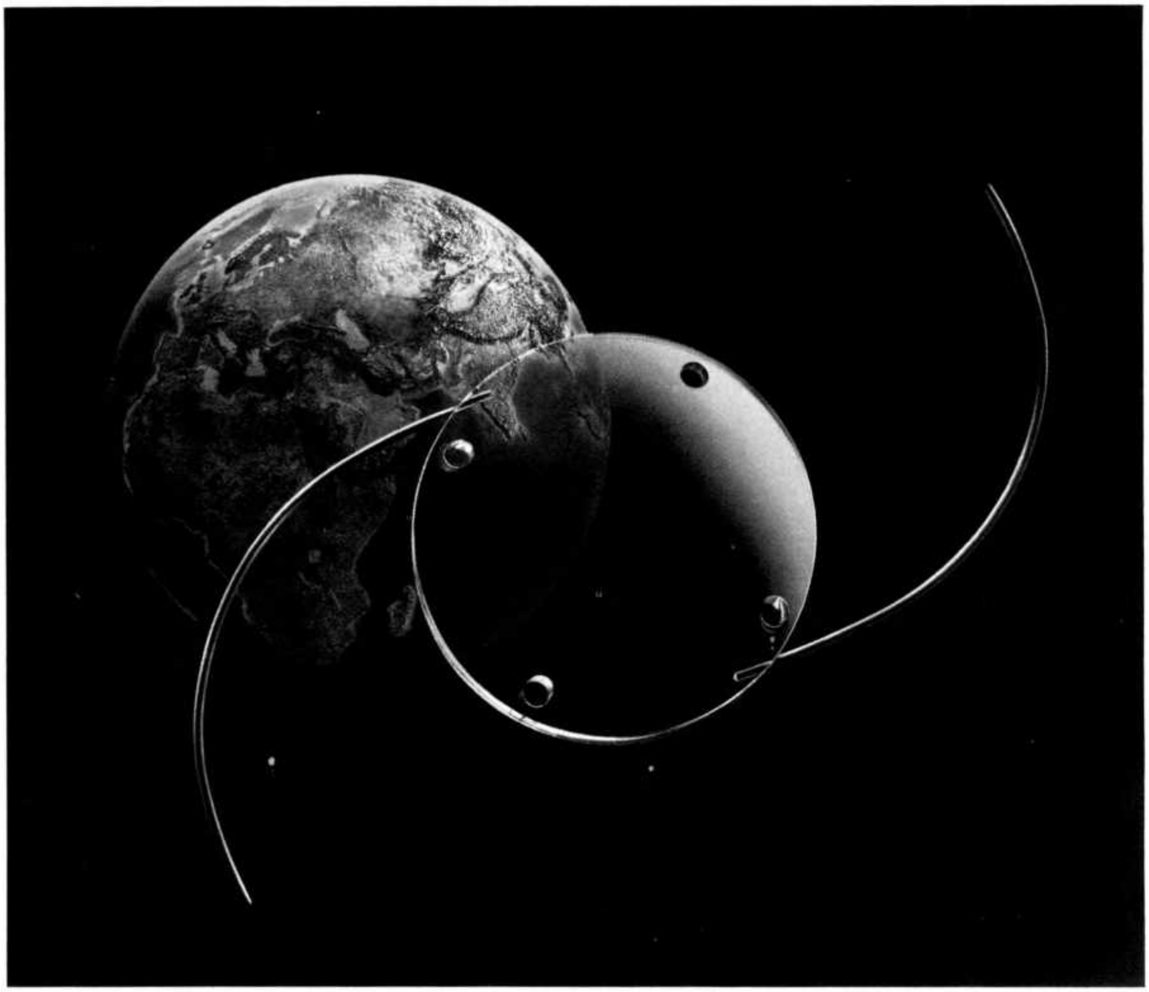

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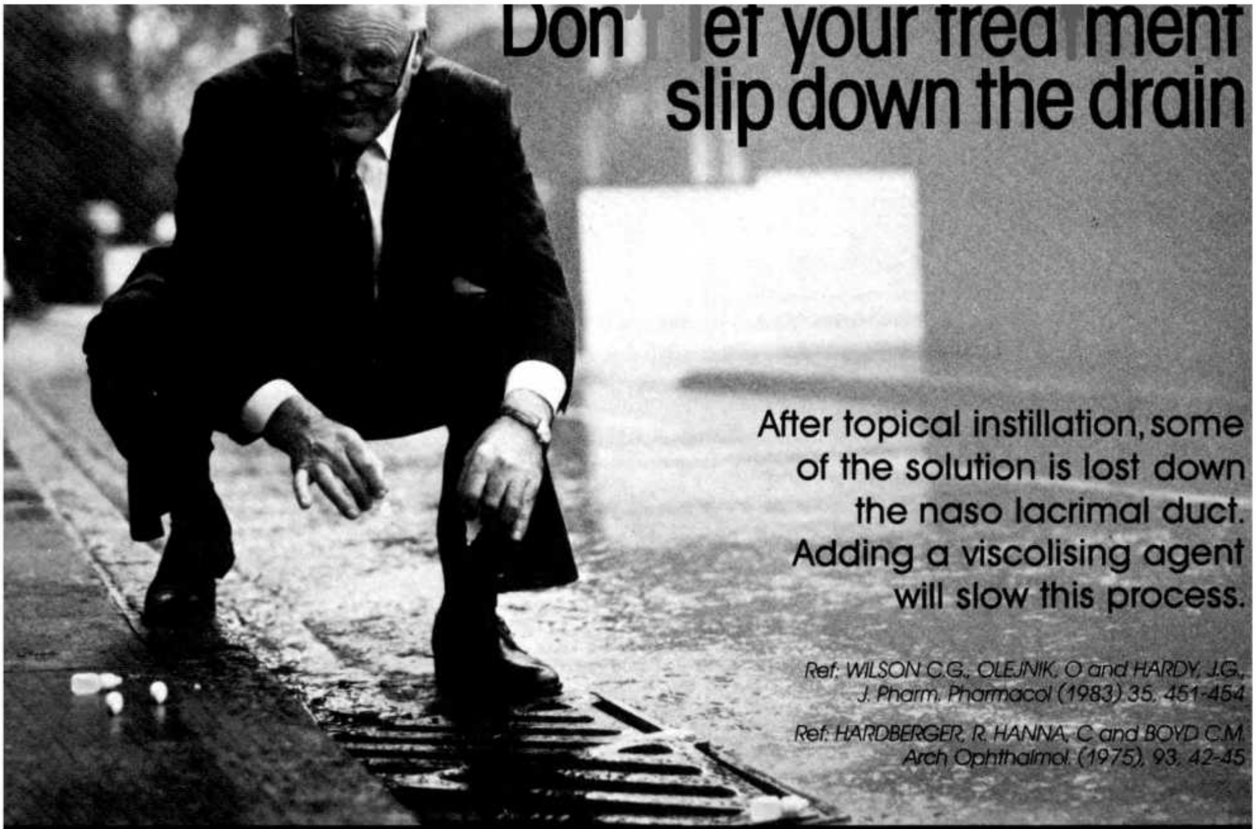

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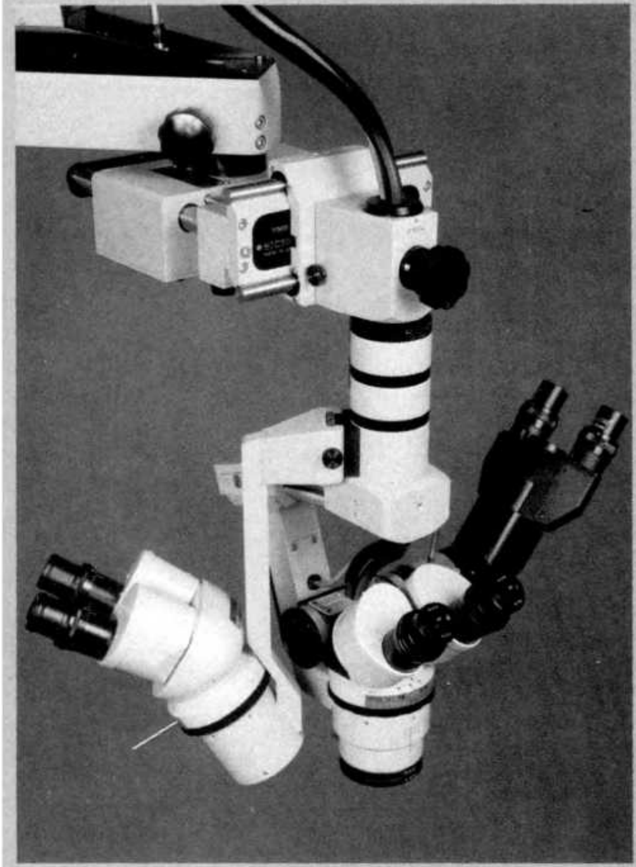

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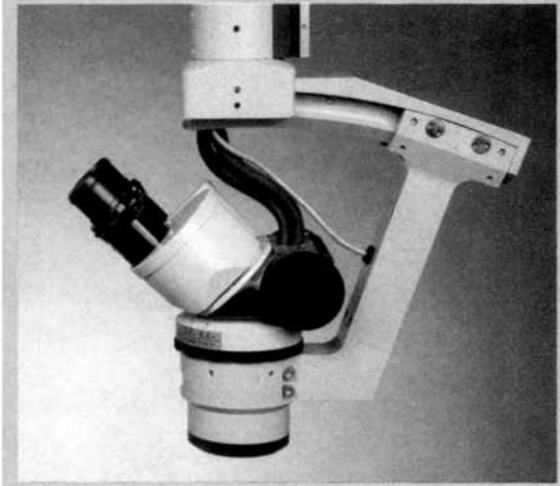

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1. Garner LL, et al, *Amer. J. Ophthalmol.* 1963 **55,** 323-327.
2. Duke Elder, WS, *Textbook of Ophthalmology* as quoted in: Moses, RA, *Adlers Physiology of the Eye,* 1975: **192.**

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British Journal of Ophthalmology, 1985, **69**, 797

Editorial: Temporary balloon buckle

In this issue of the *BJO* H Lincoff and colleagues report their experience with a temporary balloon buckle in the treatment of 100 cases of aphakic retinal detachment, mainly following intracapsular cataract extraction. Relatively simple cases were selected, and those with extensive periretinal membranes or large breaks were excluded.

The authors of this paper have once again championed the cause of performing as conservative an operation as is consistent with success by favouring the use of a local buckle in this relatively simple type of aphakic retinal detachment. This is particularly useful comment to make, because many surgeons tend to favour the use of the encirclement procedure routinely in the management of aphakic retinal detachment, even in the simple type of cases where retinal holes can be found and the retina is free of periretinal fibrous tissue. This tendency has arisen because of the erroneous concept that aphakic retinal detachments are usually associated with multiple small holes widely scattered throughout the post-oral region of the eye and that these holes may be missed if local procedures are used. Most of the more serious complications of encirclement, such as the various anterior segment ischaemic syndromes and a poor cosmetic appearance, due to ptosis and enophthalmos, are caused by high encircling buckles and excessive constriction of the globe. Appreciation of these complications has led the retinal surgeon over the years to take care not to produce an excessively high buckle. In spite of these precautions, however, the height of the eventual buckle is not always easy to control accurately, and even if the buckle height is not excessive some postoperative complications may still be encountered, such as lasting postoperative pain. The encirclement procedure has also been advocated in the belief that it may contribute to the prevention of redetachment at a later date, but there is very little evidence to substantiate this view.

In this series, although permanent reattachment was achieved in only 70 patients following the initial procedure, the authors point out that operative failure often helps to define the true position of the retinal holes. The balloon procedure could then be followed by conventional buckling operation. The procedure itself leaves a quiet eye, inflicting minimum trauma and very little disturbance, particularly in the form of interference with muscle balance. The relatively high incidence of failure with the local buckle balloon procedures has dissuaded most retinal surgeons from adopting this type of procedure routinely, but, whether or not the surgeon prefers to use the balloon or conventional full-thickness scleral buckling, the authors have made a powerful case against routinely encircling the aphakic eye, particularly when the more simple types of aphakic retinal detachment are encountered.

AHC

British Journal of Ophthalmology, 1985, **69**, 798–804

Results of 100 aphakic detachments treated with a temporary balloon buckle: a case against routine encircling operations*

HARVEY LINCOFF,[1] INGRID KREISSIG,[2] AND MATTHEW FARBER[1]

From the [1]Department of Ophthalmology of the New York Hospital-Cornell Medical Center, and the [2]Universitdts-Augenklinik, Tubingen, West Germany

SUMMARY One hundred patients with aphakic detachment were treated with temporary balloon buckles. The balloons were deflated and withdrawn after seven to 10 days. Permanent attachment depended on cryo- or laser-induced adhesions round the break. The procedure was initially successful in 79 patients. Ten retinas became detached again after the balloon was withdrawn and required a more permanent buckle. Sixty-nine retinas remained attached. The final results after additional operations were equivalent to those obtained by traditional methods, but significantly fewer complications occurred. The balloon procedure tests the validity of routinely encircling aphakic detachment.

Between June 1977 and February 1984 the authors treated 100 aphakic detachments with temporary balloon buckles in a prospective trial. The wisdom of including aphakic detachments in the balloon trial may be questioned. Aphakic detachment is thought to be associated with a special degree of vitreous traction and multiple undetectable holes in the retinal periphery.[1] For these reasons it has been almost universally treated with an encircling band. The band is supposed to counter the special traction and to wall away the small undetected breaks.

Materials and methods

PATIENTS

Each of the 100 patients who were selected for the balloon procedure had suffered a retinal detachment thought to be caused either by a single break or by a group of closely placed breaks that did not subtend a retinal arc greater than 6 mm, or 1 clock hour, as measured at the equator. The patients were consecutive and otherwise unselected. Forty-five patients were treated in Tübingen, West Germany, and 55 in New York. Ninety-four patients had undergone an intracapsular lens extraction and six an extracapsular procedure. Five of the 94 had received iris-supported intraocular lenses (Table 1). The time interval following the cataract operation was less than one week for 16 patients and more than one year for 57 (Table 2).

The detachments were confined to one or two quadrants in 63 patients and to three quadrants in 24; they were total in 13 (Table 3). The macula was attached in 45 patients, partly detached in nine, and completely detached in 46 (Table 4). The retina had been detached for less than one week in 43 patients and for more than one month in 11 (Table 5). Of the retinal breaks that could be identified 85 were flap tears, horseshoe in shape, and 10 were round. In five patients the shape of the break could not be determined; the balloon was used to probe an area of suspicion in the retina that was thought most likely to contain the superior break.[2] In 47 cases the break was beneath or adjacent to a rectus muscle, and it was necessary to place the balloon at least partly beneath the muscle. The average distance of breaks from the limbus was 13 mm (Table 6).

Some evidence of preretinal traction was found in 64 patients. Unequivocal evidence was present in 24, in the form of star folds in 11 eyes and vitreous incarcerated in the cataract wound in 13 eyes. In 40

---

*The John Milton McLean medal lecture to the Cornell Alumni, New York, 4 May 1984

Correspondence to H Lincoff, MD, Department of Ophthalmology, New York Hospital, 525 E 68th Street, New York, New York 10021, USA

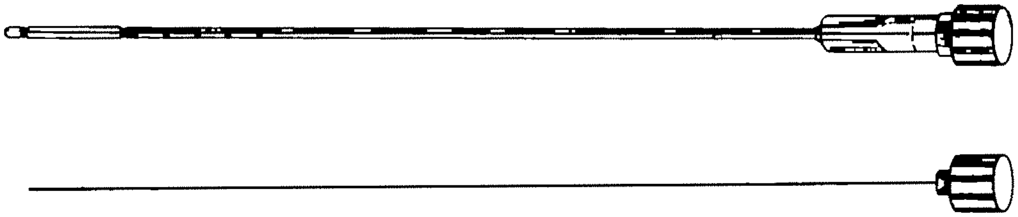

Fig. 1 *Modified balloon catheter with stylette*

Table 1 *Type of cataract operation*

Intracapsular	*Extracapsular*
94*	6

*Five patients received intraocular lenses

Table 2 *Time elapsed following the cataract operation*

<8 Weeks	*8 Weeks to 1 year*	*>1 Year*
16	27	57

Table 3 *Extent of detachment*

Quadrants	*No of patients*
1	32
2	31
3	24
4	13

Table 4 *Preoperative state of the macula*

Attached	*Partly detached*	*Detached*
45	9	46

Table 5 *Duration of retinal detachment*

<1 Week	*1 Week–1 month*	*>1 Month*	*Unknown*
43	26	11	20

Table 6 *Characteristics of the actual breaks*

Characteristic	*No.*
Shape	
horseshoe	85
round	10
unknown	5
Relationship to the muscles	
beneath a horizontal rectus	17
beneath a vertical rectus	30
Distance from the limbus (mm)	
most anterior	8
most posterior	22
average	13

Table 7 *Possible vitreous traction*

Evidence	*No*
Star folds	11
Vitreous incarceration	13
Circumferential line	40

patients the presence of a prominent circumferential line in the retinal periphery that is presumed to harbour occult tears or to be vulnerable to subsequent tearing was noted (Table 7).

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Part way through the study (in April 1982) the balloon catheter was modified by shortening it to 15 cm and inserting a wire stylette that extended to the tip of the balloon. The stylette stiffens the catheter and balloon and enables it to be directed more precisely in Tenon's space (Fig. 1).

TECHNIQUE

The technique for aphakic patients was similar to one that had previously been described.[3] Essentially, the break was localised transconjunctivally with the cryoprobe or the Urrets-Zavalia localiser and its location marked on the conjunctiva with ink. The balloon catheter with its stylette in place (in the latter part of the study) was inserted into the parabulbar space through a small puncture in the conjunctiva, was manoeuvered beneath the localising mark, and was inflated with 1 ml of saline. Acting like a large elastic explant, it closed the retinal break and caused absorption of subretinal fluid in most patients. If a larger buckle was required, additional fluid was injected after an interval long enough for the intraocular pressure to return to normal (15 to 60 minutes) or on subsequent days.

The balloons in this series were deflated and withdrawn after an average of seven days (New York) or of 10 days (Tübingen). Permanent attachment was sought by one of two methods. In Tubingen adhesions were induced by contiguous transconjunctival cryopexy around the break prior to insertion of the balloon. In New York two rows of interrupted laser applications were used to encircle the break after it came in contact with the balloon buckle, usually on the day after insertion.

All the patients underwent surgery under local anaesthesia. In New York 53 patients received a retrobulbar injection of 2 ml of lignocaine 2%, in two patients the balloon was inserted under topical amethocaine 1%. In Tubingen, from 1983, the retrobular injection of lignocaine was replaced by a subconjunctival injection limited to the quadrant of the balloon insertion.

After surgery the patients were fully mobilised. They were examined daily for one week or until the balloon was withdrawn. One week after its withdrawal they were examined again, and if the retina was attached, they were allowed to resume their usual activities. They were asked to return for follow-up examinations at one month, six months, one year, and then yearly. They were taught how to check their visual fields and were advised to return immediately if they perceived a defect. The minimum follow-up for the patients in the series was six months, the maximum was 66 months, and the average was 32 months.

Results

ANATOMICAL RESULTS

In 88 patients the balloon closed the retinal break for which it was intended. Subretinal fluid was absorbed completely in 79 (after one day in 70) (Table 8). In the other nine patients reattachment was only partial. Although the balloon closed the break for which it was intended, fluid receded to the level of a second break that had not been detected prior to the operation (Fig. 2). The shape of the residual detachment pointed to the location of the second break, and it was found in seven patients. In five of the seven the second break was buckled with a sponge, and the remaining fluid was absorbed promptly. The other two patients recovered 20/200 vision when the superior parts of their retinas became reattached after the balloon insertion, and they refused a second operation. One of the two patients with a residual inferior detachment in which the break could not be found underwent three subsequent operations; preretinal proliferation developed, and the retina became totally detached. In the other patient a shallow inferior detachment has remained for two years. Speculative surgery has been deferred because he is uniocular, has 20/25 vision, and functions as an accountant.

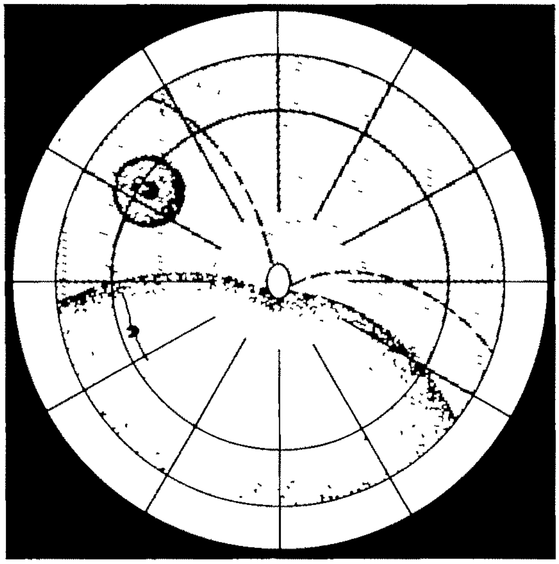

Fig. 2 *Partial reattachment after balloon insertion beneath a retinal break at 10.15 o'clock. The shape of the residual detachment points to a second break at 8.15 o'clock. Broken line indicates upper border of original detachment*

Ten of the 79 patients whose retinas became completely attached after the balloon insertion experienced redetachment after the balloon was deflated and withdrawn (Table 9). In three patients a second undetected break adjacent to the primary break was the cause; it had been temporarily closed on the edge of the balloon buckle but reopened after the balloon was withdrawn (Fig. 3). In seven patients vitreous traction on the flap of the tear overcame the laser-induced adhesion and reopened the break (Fig 4). All the redetachments occurred among the

Table 8 *Initial anatomical results of 100 balloon insertions*

Reattachment	*No.*
Complete	79
Partial	9
None	12

Table 9 *Redetachment after deflation of balloon*

Reason	*No*	*Secondary repair*	*No Reattached*
Another break adjacent	3	Sponge	3
Traction	7	sponge encircling band vitrectomy	3 2 2

Table 10 *Failure to reattach with the balloon procedure*

Reason	*No*	*No reattached with reop*
Poor placement of balloon	3	3
Another break above	5	1
Traction	3	1
Break too posterior	1	0

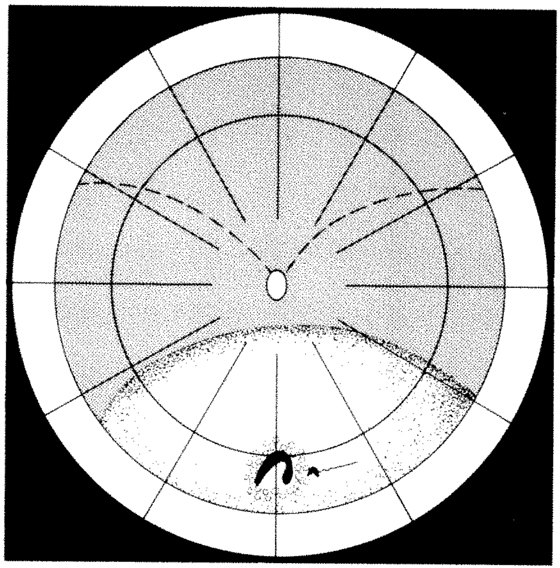

Fig. 3 *Recurrent detachment after balloon deflation caused by an undetected break that had been supported on the edge of the balloon buckle. Broken line indicates original extent of detachment.*

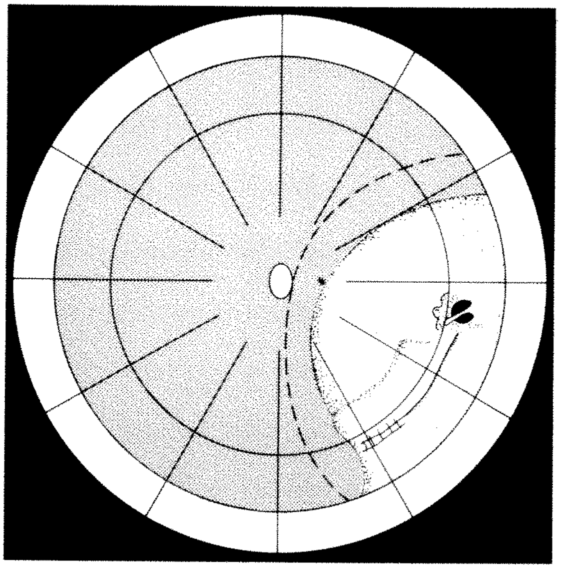

Fig. 4 *Recurrent detachment after balloon deflation caused by excessive traction on the flap of the break. Broken line indicates original extent of detachment.*

patients treated in New York, where the breaks were sealed with laser applications. All were repaired with local sponge explants and cryopexy; for two of them encircling bands were also used. Two patients eventually required a vitrectomy to sustain reattachment. None of the 79 patients whose retinas initially were reattached as the result of the balloon procedure failed to have final reattachment of the retina.

Twelve patients did not respond at all to insertion of the balloon (Table 10). In three the balloon was placed too far from the centre of the break, and an unsupported edge of the break leaked. All three retinas became reattached when the balloon was inserted in the correct place. In eight patients the procedure failed either because we never found the superior break (five patients) or because of unrelieved traction (three patients). The eight were treated with extensive circumferential buckles or encirclements, but only one retina in each category became reattached. In one patient—a diabetic with an iatrogenic break 22 mm from the limbus—the procedure failed when the balloon slipped into the retrobular space and did not cause any buckling effect. It was subsequently learned that the balloon is not suitable for breaks in the posterior pole.

Table 11 *Final anatomical results*

Reattachment	*No.*
Complete	89
Partial	3
None	8

The final anatomical result after all the procedures was 89% attached (Table 11). This compares favourably with the results obtained by Norton.[4] Our patients were selected on the basis that they were presumed to have only one break and so had a better prognosis.

VISUAL RESULTS

The visual results are displayed in scattergrams that are categorised by whether the maculas prior to surgery were attached (Figs. 5a, b), were partly detached (Figs. 6a, b), or were completely detached (Figs. 7a, b).

At three to four weeks after surgery vision in most patients with preoperative macular attachment was unchanged or slightly improved, and the results clustered around 20/20 (Fig. 5a). Improvement was probably the result of clearing of the media. Four patients lost one or two lines temporarily. Although we did not confirm it with fluorescein, the cause was probably cystoid macular oedema. At six months those four had recovered, but four others had some loss—one from uncontrolled glaucoma, two from progressive macular degeneration, and one for undefined reasons (Fig. 5b).

In all but one of the patients with partial macular detachment prior to surgery visual acuity was main-

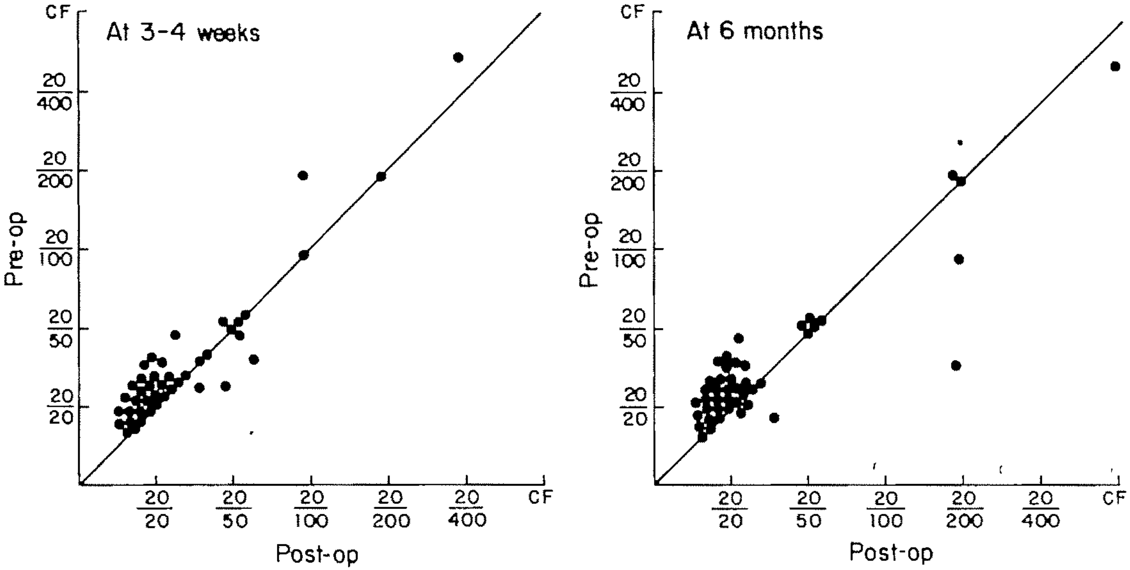

Fig. 5a Fig. 5b

Fig. 5 *Visual results in patients whose maculas were attached prior to balloon insertion. Patients whose visual acuity improved are represented by dots above the diagonal line, and those whose acuity diminished by dots below the line.* (a). *Results three to four weeks after surgery* (b) *Results six months after surgery.*

tained or improved at three to four weeks (Fig. 6a), and at six months 100% recovery was noted (Fig. 6b).

Approximately half the patients with preoperative macular detachment had improved visual acuity by three to four weeks, from vision of 20/100 or less 20/50 or better (Fig. 7a). Three patients lost some vision by the sixth month, one from ischaemic optic neuropathy and two from persistent inferior detachments (Fig. 7b).

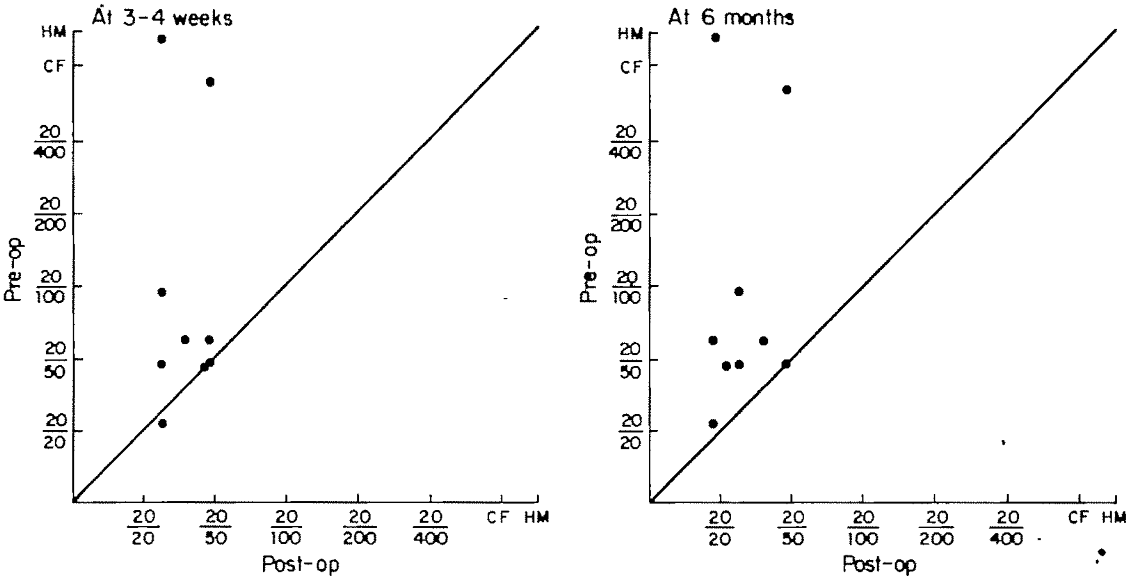

Fig. 6a Fig. 6b

Fig. 6 *Visual results in patients with partial macular detachment prior to surgery:* (a) *at three to four weeks after balloon insertion;* (b) *at six months postoperatively.*

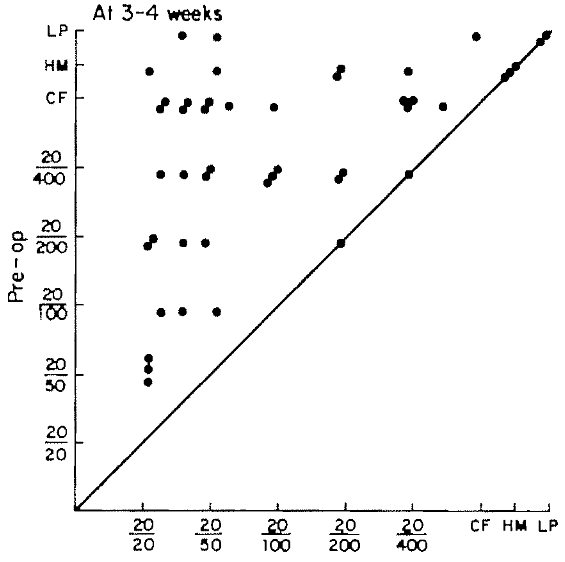

Fig. 7a

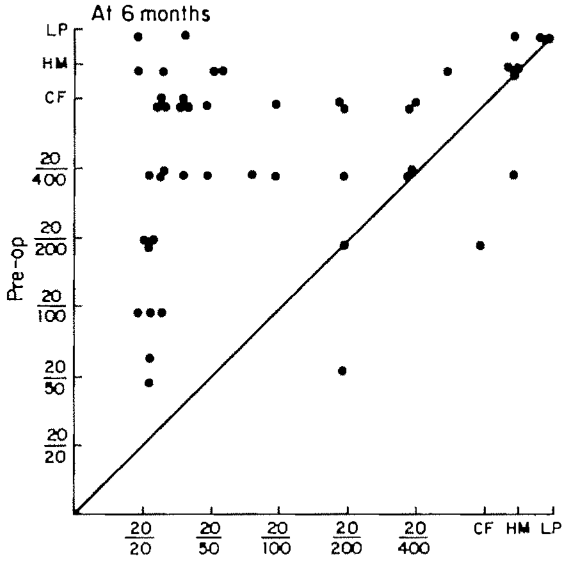

Fig 7b

Fig. 7 *Visual results in patients with macular detachment prior to balloon insertion.* (b) *at three to four weeks after surgery,* (b) *at six months postoperatively*

COMPLICATIONS

Superficial corneal erosion occurred in two patients because the catheter was improperly directed and abraded the epithelium. The corneas healed in one day when the catheter was redirected. Uveitis occurred twice. In one patient—the diabetic with the iatrogenic break near the posterior pole (see above)—it was severe. The balloon, which had slipped into the retrobulbar space, caused some venous obstruction and had to be removed on the second postoperative day. In the second patient the uveitis was mild and responded to local steroids. A macular pucker occurred in one patient who subsequently underwent multiple operations, including a vitrectomy for progressive proliferative vitreoretinopathy. Small choroidal effusions occurred in two patients and resolved spontaneously. There were no infections. It is worth noting that, although the balloon intruded beneath a rectus muscle in 47 cases and beneath a vertical in 30, the muscles nevertheless functioned normally within hours after the balloon was deflated and removed, and diplopia did not occur (Table 12).

Table 12 *Complications of the balloon insertion*

Type	*No*
Superficial corneal erosion	2
Uveitis	2
Macular pucker	1
Choroidal effusion	2
Diplopia (47)	0

Discussion

The 100 patients in this trial were presumed to have one break each of less than 6 mm and therefore constituted a group with a favourable prognosis. Nevertheless, many of them would have been treated with an encircling buckle because they were aphakic, and thus it was presumed that special tractional components as well as undetectable breaks in the retinal periphery were present. Norton[4] in his classic paper refuted the importance of special traction in aphakic detachment, but he supported the presumption of undetectable breaks in the periphery.

In our series special traction, defined here as traction sufficient to separate an unsupported laser or cryoinduced adhesion after the balloon was deflated, occurred in seven cases. That is three more than in a parallel series of phakic detachments treated with the balloon.[3] This difference is not significant by a one-trailed test with a 95% confidence interval.[6]

A better case can be made for the presumption that aphakic detachments tend to be associated with small breaks that are difficult to find. In three patients such a break occurred close to the primary break and was discovered only after the balloon was deflated and redetachment occurred. A second break below and more remote from the primary break was present in nine patients.

An encircling band or even a short sponge would have captured the adjacent breaks, but whether an encircling band as a first procedure would have closed the remote undetected breaks is questionable. In five patients in whom a break could not be found encircling buckles placed speculatively beneath the presumptive traction line in the periphery if it was present, or if not at 13 mm, succeeded in closing an undetected break only once. These results differ from Norton's experience, in which a speculative encirclement in 23 patients with undetected breaks succeeded in reattaching the retina in 20. Those figures, expressed as 87%, have had a profound effect on the management of aphakic detachment. We cannot reconcile them with our experience.

Could encirclement serve a prophylactic purpose in preventing subsequent breaks? Our series does not justify the procedure. Only one patient developed an additional break within six months after the initial reattachment.

We suggest that the routine use of encircling bands in aphakic detachment came about because, when the indirect ophthalmoscope brought the aphakic ora readily into view, magnification of the 20 dioptre lens was insufficient to show the difference between cysts and holes or tags and tears in the periphery. With the advent of the biomicroscopic technique that uses a three-mirror-contact lens in conjunction with scleral depression to study the periphery small breaks in the retinal periphery can be identified with more certainty. In this series 95% of superior breaks were found, and all but two of the inferior breaks after their presence was indicated by residual detachment. The need to wall away stretches of peripheral retina because they might harbour additional breaks has diminished.

Why not encircle anyway? First, encirclement is a four-quadrant procedure with significant complications.[4,7] If used in combination with extensive coagulation it handicaps further efforts to reattach the retina should the encirclement fail. Secondly, it promotes radial folds and so is less effective than the local use of buckles in closing retinal breaks.[8] Lastly, Yoshida *et al.*[9] have recently shown that constriction of the eye with an encircling band, even when it is limited to the 10 to 20% that we once recommended as a safe limit,[7] causes chronic ischaemia. Dobbie[10] demonstrated that encirclement diminishes the amplitude of the ocular pulse. Winter and Lipka[11] reported diminished retinal sensitivity in patients who underwent an encircling procedure.

This report recommends the use of the balloon as an initial procedure in managing selected (one break) aphakic detachments. In the series reported here the reattachment rate after one procedure was 10% less than might have been expected from local implantation of a sponge. Nevertheless, for 69 of the 100 patients the initial insertion of the balloon in conjunction with cryo or laser surgery caused permanent reattachment of the retina. For the remainder the use of the balloon defined the reasons for the retina's failure to become reattached and left a relatively uninjured eye on which to operate again.

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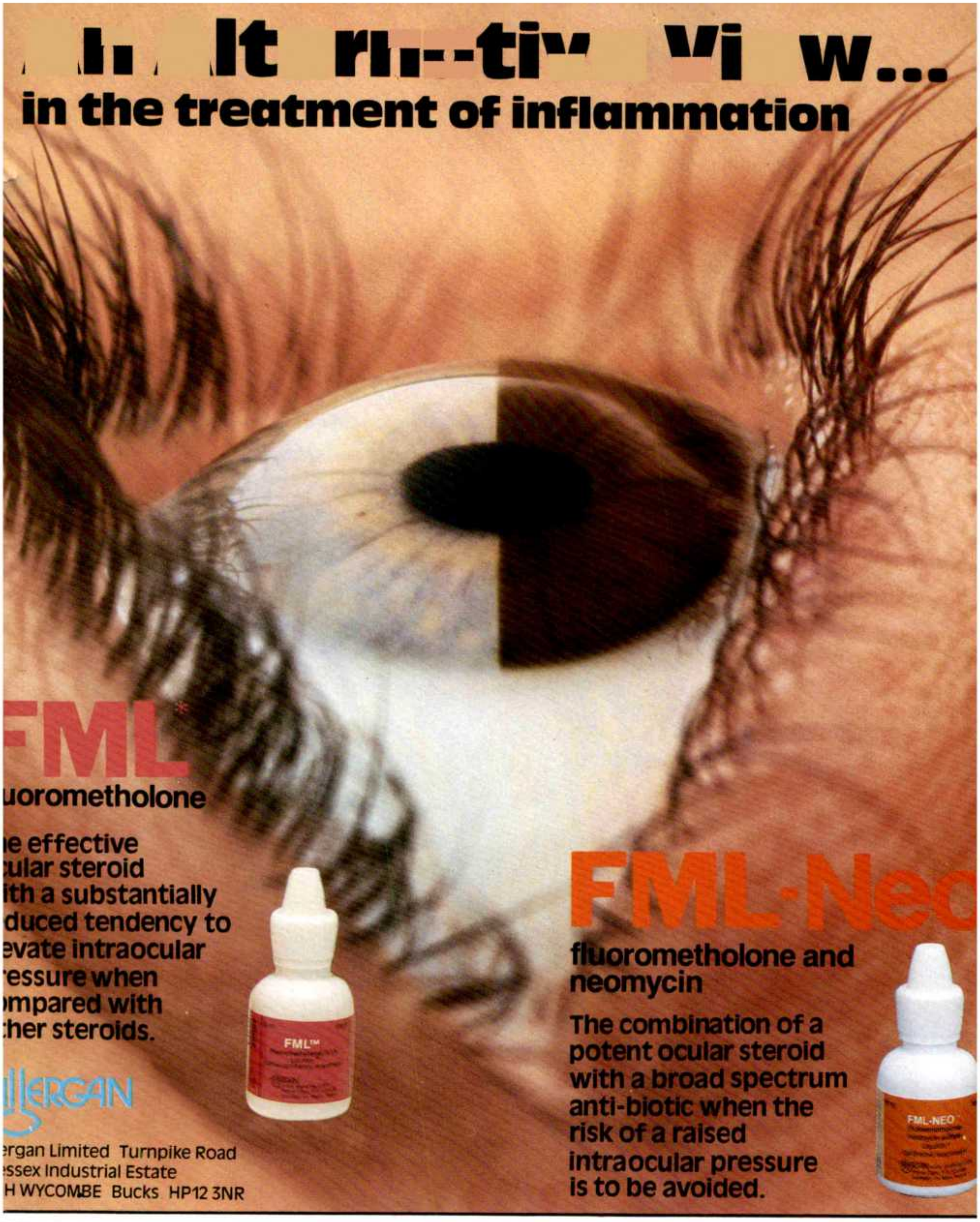

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Cilioretinal collateral circulation after occlusion of the central retinal artery

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SUMMARY Two elderly patients were noted to have unilateral central retinal arterial narrowing with cilioretinal arterial collaterals supplying the bulk of the flow to the inner retina. One patient had excellent acuity and normal pupillary reactions; the other had marked impairment of vision and an afferent pupillary defect. Both patients were asymptomatic. We suggest that these patients had gradual or partial central retinal arterial occlusion which allowed the development of a collateral arterial supply from the ciliary system.

Occlusion of the central retinal artery is most often an obvious event in which vision is abruptly lost. If the occlusion is only partial or brief, significant recovery of vision may occur. More often, however, permanent retinal damage results, and the eye remains amaurotic regardless of whether the vessels reperfuse. Retinal or anterior segment neovascularisation develops rarely, presumably because infarcted tissue does not stimulate new vessel growth. The occasional development of arterial collaterals after arterial occlusion has been recognised for many years,[1-4] most often after embolic branch artery occlusion. We report two unusual cases in which unrecognised, and presumably gradual, blockage of the central retinal artery led to the development of a nearly complete cilioretinal collateral circulation.

Case reports

CASE 1

A 69-year-old white male complained of gradual painless visual loss on the right. He denied glaucoma, amblyopia, or other previous eye disease. In 1975 he had both a coronary artery bypass graft and a left carotid endarterectomy, but he has had no strokes or myocardial infarctions and did not have hypertension. His best corrected visual acuity was 20/200 OD, 20/20 OS, and visual field testing showed no scotomas. The pupils reacted normally and equally. Applanation tensions were 15 mmHg OD, 18 mmHg OS. Both lenses had early nuclear sclerosis, with a prominent posterior subcapsular plaque present on the right accounting for the decreased vision. After extracapsular cataract extraction and lens implantation on the right, his corrected acuity was 20/20 in both eyes

Both fundi (Figs. 1A, B) showed tigroid pigmentation and normal maculae. The discs were flat and pink; a superficial hazy whitish lesion was noted just superior to the right disc. The veins were of normal caliber. On the left the arteries were mildly narrowed everywhere except over the disc, where they were markedly constricted. Prominent collaterals arose from the edge of the disc to join the arterial trunks beyond the disc margin. Fluorescein angiography (Figs. 2A, B, C) showed that the superior nasal retinal artery filled directly, but all other arterial branches received their blood supply from the ciliary vessels. No leakage or neovascularisation was seen in the late views. On the right the temporal arteries were mildly narrowed, while the nasal ones showed severe constriction. An embolus or plaque was visible at a trifurcation of the superior nasal artery near the disc margin. Fluorescein angiography (Figs. 3A, B) revealed that collaterals, unseen in the fundus photographs, were developing to the middle branch of this trifurcation.

CASE 2

A 67-year-old black female requested new glasses but had no specific visual complaints. Medical history

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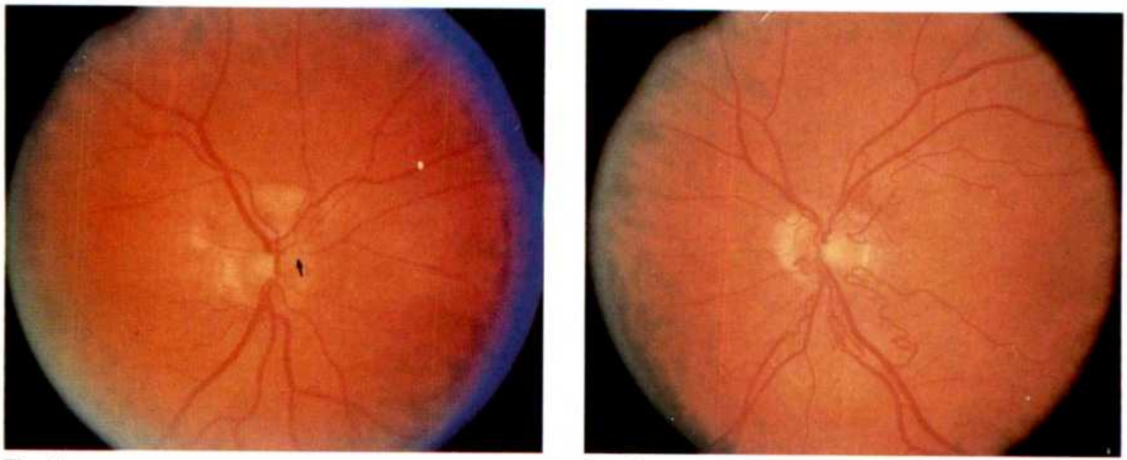

Fig. 1A

Fig. 1B

Fig 1 *Fundi of case 1.* A. *Right eye. The arteries are narrowed slightly on the temporal side and markedly on the nasal side. Arrow points to a plaque or embolus at an arterial trifurcation.* B. *Left eye. Tortuous cilioretinal collaterals supply the major arterioles.*

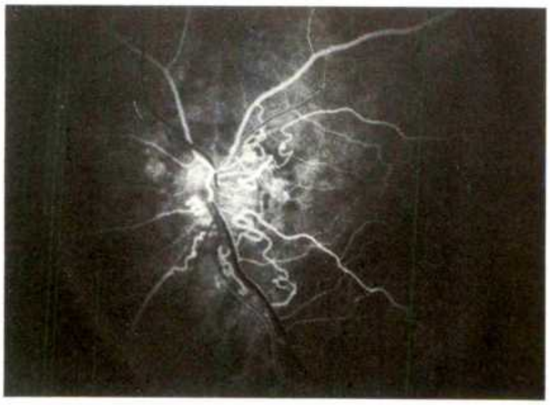

Fig. 2A

revealed moderate hypertension with poor medical compliance. *X*-rays of the orbit, optic foramen, and skull were normal. Her best corrected visual-acuity was 20/40 OD, 20/200 OS, and there was a positive afferent pupillary defect on the left. Examination of the anterior segment was otherwise unremarkable, and applanation tensions were 26 mmHg OD, 28 mmHg OS. Goldmann perimetry showed the visual fields to be full on the right but constricted with a loss of nasal field on the left.

Both fundi (Figs. 4A, B) showed normal peripheral pigmentation and macular architecture. The disc appeared normal on the right but showed pallor on the left. The vascular calibre was normal on the right, though some mild arteriosclerosis was present. On

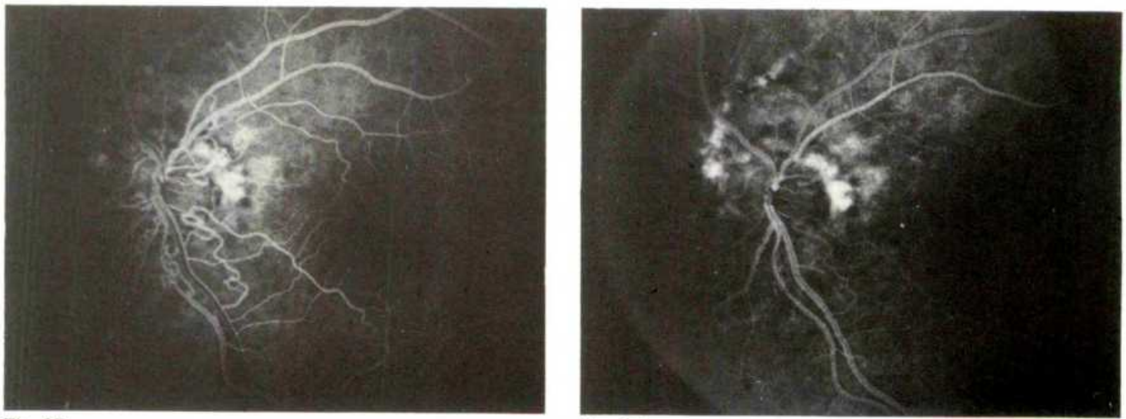

Fig. 2B

Fig. 2C

Fig. 2 *Fluorescein angiograms of the left eye of case 1. All the arterioles, except the superior nasal one, fill from the cilioretinal circulation.* A. *Arterial phase.* B. *Arteriovenous phase.* C. *Venous phase.*

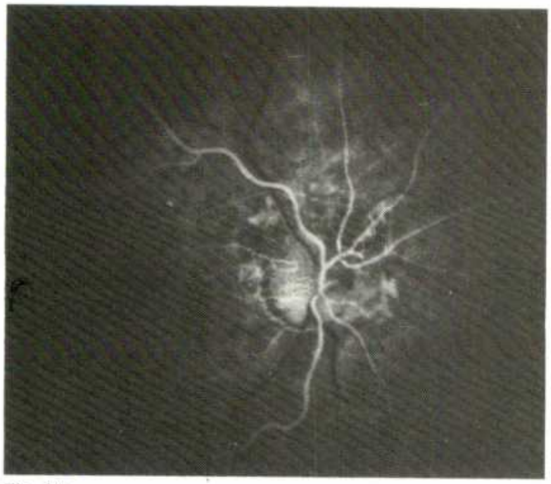

Fig. 3A

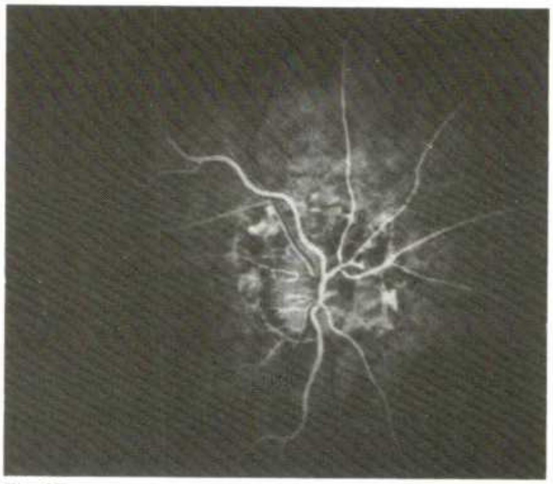

Fig. 3B

Fig. 3 *Fluorescein angiograms of the right eye of case 1. Early cilioretinal collaterals join a branch arteriole beyond the obstruction identified in Fig. 1A.* A. *Early arterial phase.* B. *Late arterial phase.*

the left the veins showed normal calibre, but the arteries were moderately narrowed. Over the disc the branch arteries from the central retinal artery became mere threads and were joined by collaterals arising from the edge of the disc. Fluorescein angiography of the left eye (Figs. 5A, B, C) showed that there was a small degree of filling from the central retinal artery, but the arteriolar collaterals supplied much of the arterial flow. There was no neovascularisation or leakage of fluorescein.

Discussion

These cases are unusual in that nearly complete occlusion of the central retinal artery occurred without severe loss of vision. Either the obstruction must have developed gradually, so that there was no episode of sudden visual loss, or the initial episode of obstruction was overlooked and the vessels opened sufficiently to allow partial recovery. As the central retinal artery narrowed, or after its occlusion, fine capillary connections between the ciliary and retinal circulations expanded to augment the blood flow to the retina. Remarkably, the visual acuity of the affected eye in case 1 remained 20/20. This was in fact the patient's good eye; his presenting complaint was poor vision from the cataract on the right. The visual acuity of the affected eye was 20/200 in case 2, and

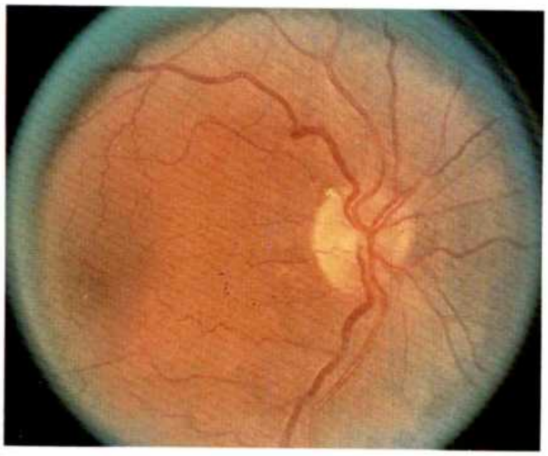

Fig. 4A

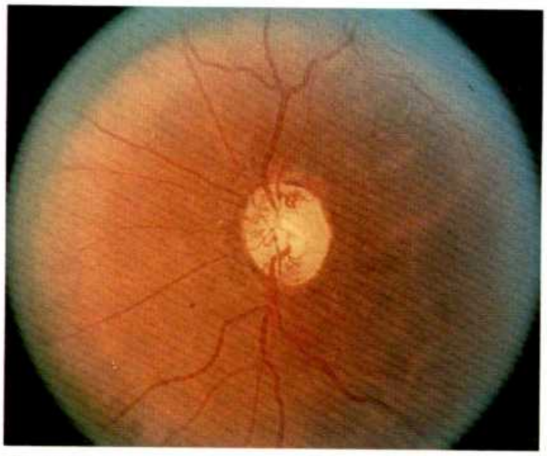

Fig. 4B

Fig. 4 *Fundi of case 2.* A. *Right eye.* B. *Left eye. There is marked narrowing at the origin of the retinal arteries, and cilioretinal collaterals bypass the constriction.*

there was a mild afferent pupillary defect, suggesting that a greater degree of inner retinal damage occurred before sufficient circulation could be established.

The development of arterial collaterals can be observed experimentally within days after occlusion of retinal vessels with emboli.[2] Indeed most of the clinical descriptions have shown collaterals circumventing a visible blockage of a retinal artery, either central or peripheral. Jensen[1] described the appearance of such collaterals within a few weeks, and their formation probably begins very soon after occlusion. Why are they not seen more frequently? Several factors probably contribute to their scarcity. Firstly, if the vascular occlusion is severe (as is often the case), vascular tissue will be damaged and unable to support collateral circulation. Secondly, if the inner retinal neurons are severely damaged, metabolic demand may be insufficient to justify collateral formation even if the vasculature survives. Thirdly, if the blockade is relieved (for example by passage of an embolism or relief of spasm) the need for collateral circulations will be eliminated. Fourthly, if the pathophysiology of occlusion included more proximal vascular disease, such as occlusion of the internal carotid artery, there might be concomitant ischaemia of the choroidal circulation and insufficient flow to support collaterals. For example, chronic retinal ischaemia from carotid occlusive disease may lead to a fundus picture of venous congestion and stasis,[5] possibly on the basis of ischaemic damage to the vasculature. Since the site of occlusion is outside the orbit, the ischaemia is not correctable by the formation of cilioretinal collaterals.

Only if these various conditions are absent, if a relatively focal blockage exists in the retinal arterial tree, and if sufficient retinal and choroidal flow exists to maintain at least minimal retinal and vascular viability, will collaterals be able to form. This set of conditions could exist after an embolic block which still allows a trickle of blood to get through. Indeed this seems to be the situation in the right eye of case 1, in which a branch arteriole, partly occluded by an embolus, is just beginning to develop collaterals. Alternatively, gradual closure of the retinal vessel by sclerosis or thrombus formation, or by recurrent tiny emboli, might encourage the widening of collateral channels. Case 1 shows clearly that once collaterals have developed, good retinal function can be maintained through a ciliary supply. The existence of occasional patients with absent retinal arteries and a congenital cilioretinal arterial supply to the retina

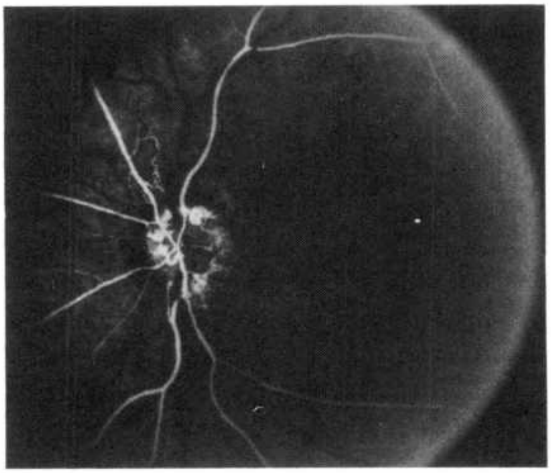
Fig. 5A

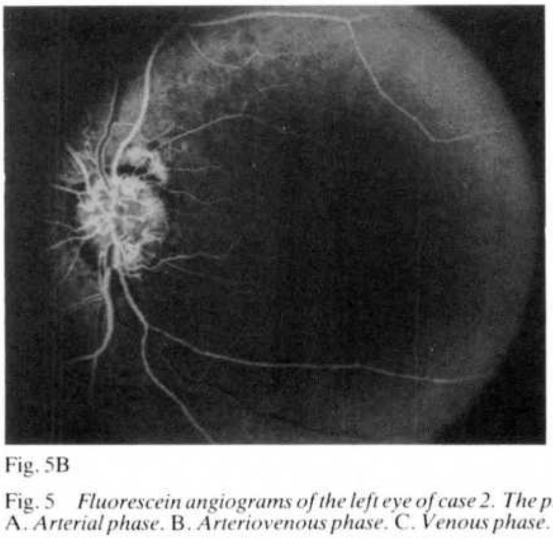
Fig. 5B

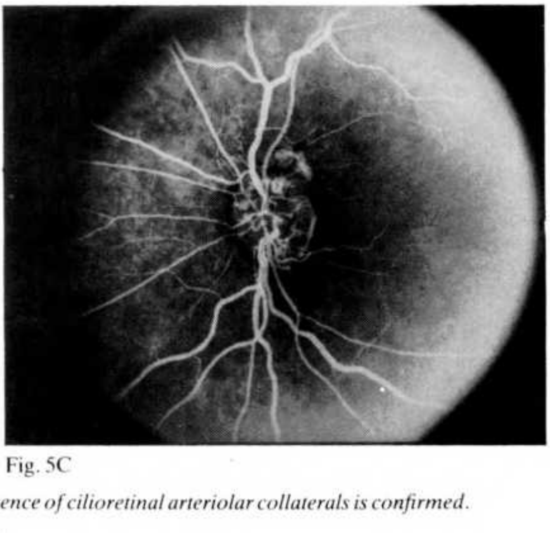
Fig. 5C

Fig. 5 *Fluorescein angiograms of the left eye of case 2. The presence of cilioretinal arteriolar collaterals is confirmed.* A. *Arterial phase.* B. *Arteriovenous phase.* C. *Venous phase.*

confirms this observation. We consider the lesions in our patients were clearly acquired and not congenital.

In cases where there is no history of sudden visual loss, arterial collaterals must be distinguished from other vascular abnormalities. Venous collaterals may develop in conditions such as central retinal vein occlusion or an optic nerve sheath mengingoma which blocks venous drainage,[6] but the venous nature of the collateral circulation should be evident on fluorescein angiography. Arterial collaterals fill immediately as fluorescein enters the eye and before the venous phase has begun, whereas venous collaterals will be seen to fill during the venous phases of the angiogram. Many vascular anomalies of the retina and optic disc have been described, such as familial arteriolar tortuosity[7] or prepapillary loops.[8] These are unlikely to be confused with the characteristic pattern formed by tortuous collaterals arching over a zone of narrowed or absent retinal artery. Collateral vessels may resemble neovascularisation, and this distinction is important because the presence of neovascular growth would signify continued ischaemia and a possible need for photocoagulation therapy. Furthermore both may be present concomitantly.[9] Retinal and optic disc neovascularisation is rather rare after retinal artery occlusion and more often seen in the presence of carotid occlusive disease.[9,10] However, since carotid disease is not uncommon in patients with retinal artery occlusive disease, separating the contribution from each entity may not always be easy. New vessels, like collaterals, do not ordinarily develop after a complete retinal artery occlusion, because little viable retinal tissue remains. If the occlusion is more gradual, or conditioned by preexisting central ischaemia, then neovascularisation of the retina and anterior segment may develop. The diagnosis can be confirmed by fluorescein angiography, which will show a leakage of dye from neovascularisation but not from arterial collaterals (as in these present cases), which retain tight junctions.

Gary Lissner, MD, allowed us to report case 2

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Natural history of fibrocellular epiretinal membranes: a quantitative, autoradiographic, and immunohistochemical study

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SUMMARY Quantitative, autoradiographic, or immunohistochemical light microscopy was conducted on 85 surgically excised epiretinal membranes to investigate the activities of component cells and the natural history of the extraretinal scars. Membranes of less than four months' clinical duration ('early' membranes) contained significantly more cells than 'late' membranes, while collagen was more abundant in the older specimens. No correlation was established between membrane opacification and either the cellularity or the collagen content of the membranes. Epiretinal membranes had some features in common with healing skin wounds, but the activities of cells in the epiretinal membranes were relatively protracted and disordered. Fibronectin was found to be a significant component of epiretinal membranes and therefore represents a target at which pharmacological intervention could be aimed.

Contractile epiretinal membranes (ERMs) produce tangential traction on the underlying retina, with consequent inner retinal striation or full-thickness folding as seen in macular pucker and massive periretinal proliferation (MPP). Because ERMs contain fibroblast-like cells and collagen[1] they have been likened to the scars of healing wounds elsewhere in the body.[1 2] Healing wounds are noted for early migration and proliferation of cells[3] and production of extracellular materials, including the glycoprotein fibronectin (FN)[4 5] Fibroblasts cause wound contraction by virtue of their intracytoplasmic contractile filaments, including actin,[6 7] and they also synthesise collagen to produce a fibrous scar.[8 9]

Some of the maturation processes documented in healing wounds have been described in experimental models of ERM formation, but most studies of human ERMs have been orientated towards determining the origins of the cells within the ERMs. Consequently there is little information concerning the natural history of ERMs in man and the behaviour of contributing cells at each stage of membrane development. Furthermore, apart from ultrastructural descriptions of microfilaments[10-13] and limited histochemical studies[14-16] we know very little about actin within epiretinal cells; equally, the production and distribution of FN in ERMs have not been reported. We have therefore undertaken a detailed study of a large number of ERMs removed during closed microsurgery for macular pucker and MPP including (1) thymidine autoradiography and cell quantitation in order to provide data on the proliferative capacity and fate of cells in ERMs, (2) autoradiographic investigations of proline and glucosamine uptake in order to determine the synthetic capabilities of cells in ERMs, and (3) an immunohistochemical study of the distribution of actin and FN in ERMs with special reference to their association with specific cell types.

Material and methods

Eighty-five ERM specimens were obtained during closed microsurgery for macular pucker (50 eyes) or MPP (35 eyes). Aetiological associations, an estimate of clinical duration (based on the history of visual distortion, retinal detachment, etc.) and the biomicroscopic appearance of each ERM were recorded The ERMs were arbitrarily grouped into those of less than four months' duration (*early*

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ERMs) and those of over four months' duration (*late* ERMs). Where the clinical duration of an ERM could not be estimated with any degree of accuracy, the specimen was discarded from the study.

LIGHT MICROSCOPY AND CELL COUNTING

Forty-five ERMs (21 *early* and 24 *late*) were fixed in 3% buffered glutaraldehyde, postfixed in 1% osmium tetroxide, dehydrated in graded alcohol, and embedded in Araldite. Three 1 µm thick sections were obtained from each plastic embedded membrane. Intervals of 10 µm were left between each section to avoid individual cell nuclei being counted twice. After toluidine blue staining the total number of cell nuclei and the number of inflammatory cell nuclei (including macrophages, polymorphonuclear leucocytes, and lymphocytes) were counted under an oil immersion lens in each section. The assessments were made by two observers (PSH and IG) independently and subsequently averaged (intra- and interobserver error 10%) The area of each section was assessed by means of a photographic image projected on to a 'random-dot' grid, and a cumulative value of total and inflammatory cell nuclei per unit area was derived from the three sections. For statistical comparisons between *early* and *late* ERMs Student's *t* test and the Mann-Whitney U test were adopted.

In addition the proportion of cells showing features of degeneration or necrosis, such as excessive lipid accumulation in the cytoplasm or loss of nuclear staining (karyolysis), was assessed for each ERM. Finally the proportion of collagen in each ERM was judged as follows: minimal collagen +, moderate collagen ++, and abundant collagen +++. Further, the arrangement of the collagen (that is, whether the fibres formed a disorganised network or were arranged in bundles) was noted

CLINICAL GRADING

Great difficulty was experienced in grading the degree of opacification of ERMs, not least because of the wide variation in contour, extent, and thickness of the contracted membranes and potential confusion with opacification of the underlying retina, whether due to axoplasmic stasis in the inner retina or oedema of the outer retina. This latter problem was so dominant in MPP cases that we elected to confine our clinicopathological correlation to those cases of macular pucker in which there was good photographic documentation (23 cases). One of us (DMcL) independently ranked the epimacular membranes (from the most transparent to the most opaque) according to the predominant degree of obscuration of the blood columns in the underlying retinal vasculature. This serial grading was then compared with the total cell density and also with a similar serial grading of collagen content (from the least to the most abundant) in these 23 biopsied epimacular membrane specimens. The results were subjected to statistical analysis by the Spearman-Rank correlation matrix.

AUTORADIOGRAPHY

After surgical removal 26 ERM specimens were immediately transported to the laboratory at 4°C in medium 199 (Wellcome, Beckenham, Kent). The tissue was incubated at 37°C for 24 hours in a Leighton tube incorporating 1 ml of medium 199 enriched with 10% fetal calf serum and glutamine. The organ culture media contained one of the following radiolabelled substrates:

(1) 30 µCi of methyl-^{3}H thymidine (specific activity 26·0) as a marker for cells undergoing DNA synthesis (4 *early* and 10 *late* ERMs); (2) 100 µCi of methyl-^{3}H proline (specific activity 21·0) to indicate cells producing proteins including collagen (4 *early* and 3 *late* ERMs), or (3) 30 µCi of D-6-^{3}H glucosamine hydrochloride (specific activity 34·6) to label cells synthesising glycosaminoglycans, proteoglycans, and glycoproteins,[17] including fibronectin (3 *early* and 2 *late* ERMs). All radiochemicals were supplied by Amersham International PLC, Amersham, Buckinghamshire, England.

The ERMs were subsequently fixed and embedded in Araldite as described above. Sections 1 µm thick were placed on gelatin covered subslides, coated with K5 nuclear emulsion (Ilford, Mobberly, Cheshire), and kept at 4°C. After being developed with D-19 developer (Kodak, Hemel Hempstead, Hertfordshire) the sections were counterstained with toluidine blue; at least 12 sections per membrane were studied. The incorporation of label was judged as follows: background −, minimal +, moderate ++, and avid +++

IMMUNOHISTOCHEMISTRY FOR ACTIN AND FIBRONECTIN

Fourteen specimens (7 *early* ERMs and 7 *late* ERMs) were investigated immunohistochemically by means of antiactin and anti-FN immunofluorescence or immunoperoxidase staining as previously described.[18-20] The distribution and intensity of actin and FN immunostaining were noted. For both, the staining intensity was graded as follows: background −; weak +; moderate ++, and intense +++. 'Intense' corresponded for actin to the staining seen in extraocular muscle or, for FN, to the reaction associated with five-day rabbit skin wounds.

IMMUNOHISTOCHEMICAL CELL-TYPING

With 7 µm wax or 10 µm frozen serial sections, antibodies to cytoskeletal proteins identified aggre-

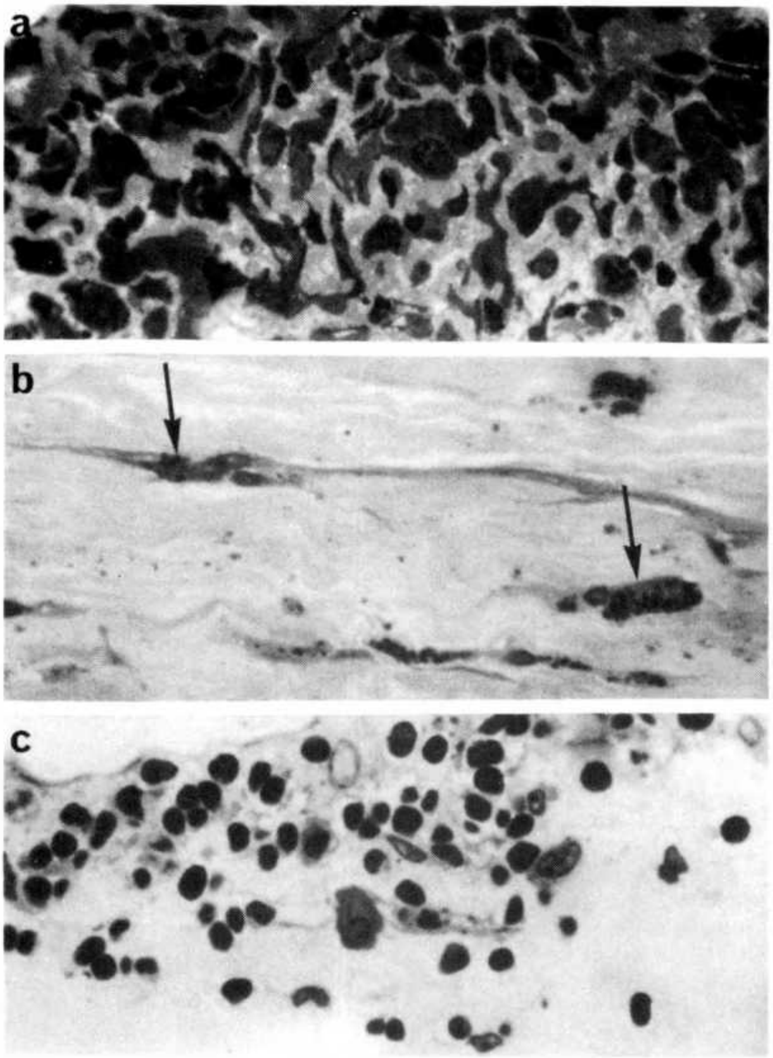

Fig. 1 *Sections 1 μm thick stained with toluidine blue.* (a) Early *ERM. Hypercellular membrane in which collagen is sparse.* (b) Late *ERM. Abundant collagen with bundle formation. Only a few cells are present, and several of these show lipid accumulation in the cytoplasm (arrows).* (c) *Epimacular membrane associated with pars planitis. Although the ERM appears to be hypercellular, the majority of the cells are inflammatory cells, including lymphocytes and monocytes. (×560).*

gates of cells of similar derivation within those 14 ERMs studied immunohistochemically for actin and FN; scattered and isolated cells were excluded from the analysis. Specific antibody labelling of glial fibrillary acidic protein (GFAP) identified an aggregate of glial cells in each of 12 ERMs[19]; antikeratin and antiprekeratin immunostaining revealed an aggregate of epithelial cells (presumed to be of pigment epithelial cell origin) in seven ERMs[20]; and aggregates of fibroblast-like cells showing negative immunostraining for glial and epithelial cells (hereafter called 'fibroblasts') were available for study in 13 ERMs. Comparison of actin and FN staining intensities in all three types of cellular aggregate (glial cells, epithelial cells, and fibroblasts) was possible in six ERMs. In a further six ERMs two types of cellular aggregate were available for comparison, while in the two remaining ERMs only fibroblast aggregates were present.

Results

LIGHT MICROSCOPY AND CELL COUNTING

The mean total cell nucleus count per unit area (± standard deviation) in the 21 *early* ERMs (Fig. 1a) was 16·6±7·2; by contrast, the 24 *late* ERMs (Fig. 1b) had a mean of 9·5±5·8, and the difference was significant (student's t test, $p<0·001$; Table 1). Of the ERMs associated with rhegmatogenous retinal detachment, the mean total cell count in *early* ERMs (13 specimens) was 18·7±7·7 and in *late* ERMs (7 specimens) was 9·3±4·2 (student's t test, $p<0·01$).

Table 1 *Clinical details and quantitative results of 45 ERMs*

	Aetiology	*No of ERMs*	*Cell counts per unit area ± SD*		*Collagen*			
			Total	*Non-inflammatory*	+	++	+++	*Bundles*
Early epimacular membranes (11)	RRD	4	18·9±12·3	17·6±12·6	2	2	0	1
	Other*	7	12·8± 5·5	11·2± 5·2	3	4	0	4
Early MPP membranes (10)	RRD	9	18·5± 5·7	16·5± 5·7	9	0	0	2
	Other*	1	17·0	15·7	1	0	0	0
Total		21	16·6± 7·2	15·1± 7·3	15 (72%)	6 (28%)	0	7 (33%)
Late epimacular membranes (19)	RRD	6	8·7± 4·1	7·3± 4·1	1	3	2	5
	Other*	13	10·4± 7·2	6·6± 2·7	1	8	4	8
Late MPP membranes (5)	RRD	1	13·5	12·6	1	0	0	1
	Other*	4	7·1± 3·1	5·4± 2·7	0	2	2	4
Total		24	9·5± 5·8	7·1± 2·9	3 (13%)	13 (54%)	8 (33%)	18 (75%)

MPP=massive periretinal proliferation RRD=rhegmatogenous retinal detachment SD=standard deviation

*Other aetiological associations	Perforating trauma.	3 early 7 late (5 epimacular 5 MPP)
	Blunt trauma	0 early 1 late (epimacular)
	Idiopathic	2 early 1 late (epimacular)
	Pars planitis	1 early. 3 late (epimacular)
	Nodular telangiectasis[21]	0 early 3 late (epimacular)
	Eales disease:	1 early 1 late (epimacular)
	Cone dystrophy.	1 early. 0 late (epimacular)
	Branch vein occlusions·	0 early: 1 late (epimacular)

+++=Abundant collagen ++=Moderate collagen +=Minimal collagen

Inflammatory cells were present in all ERMs, but their numbers showed considerable variation between individual specimens; they were most prominent in ERMs complicating pars planitis (Fig. 1c). *Late* ERMs contained proportionally more inflammatory cells (mean 21·6±20·0%) than *early* ERMs (mean 11·5±5·7%). However, the standard deviations are particularly high, and thus there was no significant difference between the two groups (Mann-Whitney U test). When inflammatory cells were excluded, the mean count for the 21 *early* ERMs was 15·1±7·3 and for the 24 *late* ERMs 7·9±2·9 (student's t test, $p<0·001$). Degenerated (Fig. 1b) and necrotic cells represented 24·8±14·2% of the total non-inflammatory cells in *early* ERMs and 29·8±16·8% in *late* membranes.

Fifteen of the 21 *early* ERMs (72%) contained minimal amounts of collagen, and in none of the other six *early* ERMs was collagen abundant. By contrast, only three of the 24 *late* ERMs (13%) had a minimal collagen content, while eight *late* ERMs (33%) contained abundant collagen. Bundles of collagen were seen in seven *early* ERMs (33%) and 18 *late* ERMs (75%) (Table 1).

CLINICOPATHOLOGICAL CORRELATION OF THE 23 SERIALLY GRADED EPIMACULAR MEMBRANES

Spearman Rank testing (Table 2) demonstrated that there was no correlation between the clinical opacification of our ERMs and either the collagen content or cellularity of the specimens. However, the test confirmed an inverse relationship between collagen content and cellularity ($p<0·01$), as would be expected from our other quantitative results. The total cell count correlated positively with the total non-inflammatory ($p<0·01$) and the total inflam-

Table 2 *Spearman rank correlation matrix for 23 serially graded epimacular membranes*

Variables	*Opacity*	*Collagen*	*Total cells*	*Inflammatory cells*	*Non-inflammatory cells*
Opacity		−0·3271	0·1567	0·1860	−0·0969
Collagen			−0·6600*	−0·4440	−0·6543*
Total cells				0·7626*	0·8136*
Inflammatory cells					0·4284
Non-inflammatory cells					

*Significant at or better than $p<0·01$

Table 3 *Proline and glucosamine autoradiography*

P/G (Figure)	*MP/MPP*	*Aetiology*	*Approximate ERM duration (months)*	*Overall avidity of label incorporation*
P—3a	MPP	RRD	1	–
P—3b	MP	BT	3·5	+
P—3c	MP	PT	3·5	+
P—3d	MPP	RRD	4	+++
P—3e	MP	RRD	4·5	++
P—3f	MPP	RRD	6	++
P—3g	MP	RRD	8	+
G—4a	MPP	PT	3	++
G—4b	MPP	RRD	3·5	+ to ++
G—4c	MP	RRD	4	+ to ++
G—4d	MP	ROP/RRD	4·5	–
G—4e	MPP	RRD	8	++

*Blood vessels show glucosamine uptake by endothelial cells.
MP=Macular pucker. MPP=Massive periretinal proliferation. RRD=rhegmatogenous retinal detachment. BT=blunt trauma. PT=perforating trauma. ROP=retinopathy of prematurity. NCP=no cells present. ILL=inner limiting lamina. P=proline. G=glucosamine.

matory ($p<0.01$) cell count respectively, because the total cell count comprised the latter two cell subsets.

THYMIDINE AUTORADIOGRAPHY

Three of the four *early* ERMs contained cells which incorporated labelled thymidine in organ culture (Fig. 2). By contrast only one of the 10 *late* ERMs contained cells which took up ^{3}H thymidine. In all four specimens which incorporated ^{3}H thymidine labelled cells were distributed throughout the tissue, and fewer than 5% of the total cells present were found to be labelled.

PROLINE AUTORADIOGRAPHY

Although all ERMs incubated with ^{3}H proline contained cells which incorporated the label, there was

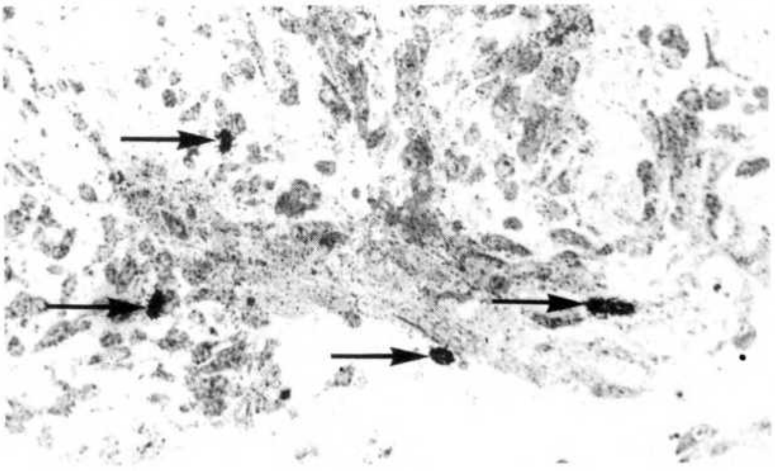

Fig. 2 *^{3}H thymidine autoradiographic section 1 µm thick, counterstained with toluidine blue. The* early *membrane is hypercellular, and four cell nuclei are seen to have incorporated the label (arrows). (×280).*

Overall distribution of label	*Avidity of incorporation of label by spindle cells*	*Avidity of incorporation of label by cuboidal cells*	*Histological description and comment*
Patchy	–	– to +	Hypercellular ERM, chiefly spindle cells on ILL with little collagen
Patchy	– to ++	– to ++	Hypercellular ERM with spindle cells in collagen and layers of cuboidal cells
Patchy	+ to +++	+ to +++	Hypocellular, collagenous ERM, spindle cells predominate
Uniform	+++	NCP	Hypercellular ERM of spindle cells in collagen on ILL
Patchy	++ to +++	+++	Collagenous ERM with prominent spindle and cuboidal cell element
Patchy	–	+ to +++	Collagenous ERM with cuboidal cells predominating over spindle cells
Patchy	– to +++	+++	Spindle and inflammatory cells on collagen Few cuboidal cells on ILL
Patchy	– to ++	++ to +++	Hypercellular ERM with prominent spindle cells and large focus of cuboidal cells
Patchy*	+ to ++	– to ++	Cellular, little collagen and occasional blood vessels
Patchy	– to ++	+ to ++	Hypercellular, mainly spindle cell, ERM with layer of cuboidal cells
Patchy*	– to +	NCP	Hypocellular, collagenous ERM with occasional spindle cell and blood vessels
Patchy	–	+ to +++	Collagenous ERM, but many cuboidal, spindle, and inflammatory cells

+++ = Intense labelling
++ = Moderate labelling
+ = Weak labelling
– = Background labelling

considerable variation in the overall intensity of cell labelling both between and within membranes (Table 3 and Fig. 3). The results suggest that very *early* (Figs. 3a–c) and very *late* ERMs (Fig. 3g) did not incorporate as much ^{3}H proline as do 'middle age' (Figs. 3d–f) specimens. However, our series is too small to draw any firm conclusion about the ERM age and ^{3}H proline uptake. Inflammatory cells showed only minimal ^{3}H proline incorporation. By contrast both elongated spindle-shaped cells and plump (cuboidal) cells with prominent cytoplasm and large pale-staining nuclei incorporated the label to varying degrees (Fig. 3). Where both cell types were present in an individual membrane, cuboidal cells appeared to take up ^{3}H proline more avidly than spindle-shaped cells. This observation held true for cuboidal cells both within layers and foci or as scattered cells in collagen. Also notable was the great variation in ^{3}H proline uptake between cells of a similar morphological appearance within individual ERMs. This variation did not appear to be due to defects in label penetration of the specimens, since ^{3}H proline incorporation was found in cells at all depths of the tissues.

GLUCOSAMINE AUTORADIOGRAPHY

No obvious association between ^{3}H glucosamine uptake by specimens and ERM duration was observed (Table 3 and Fig. 4). There was, however, considerable variation in label incorporation in morphologically different cells. Overall, inflammatory cells showed minimal incorporation of ^{3}H glucosamine and spindle-shaped cells showed less avid incorporation than cuboidal cells, especially where the latter were arranged in layers (Fig. 4a). Two of our ERMs had a minor vascular component (Figs. 4b, 4d) and the endothelial cells of these vessels showed ^{3}H glucosamine uptake. Again, label penetration to all depths of the specimens was observed.

IMMUNOHISTOCHEMISTRY FOR ACTIN AND FIBRONECTIN

Early vs. late ERMs

Table 4 shows that in both *early* and *late* ERMs, intense actin staining was not prominent (Fig. 5a) There was no substantial difference in overall staining intensity for actin between cells in *early* and *late* ERMs (Table 4). Actin staining at greater than background levels was restricted to patches of cells in eight ERMs but was evenly distributed throughout the cells in three ERMs. In the remaining three *late* ERMs obvious staining was present only within small

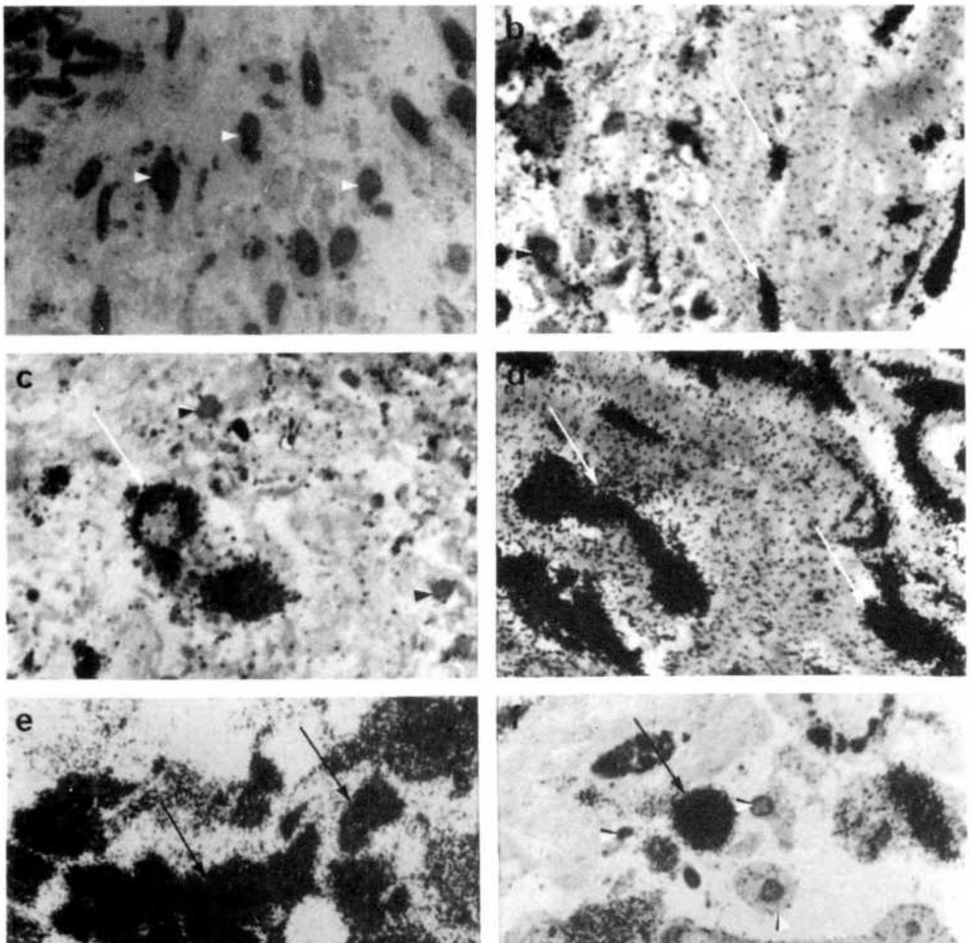

Fig. 3 *^{3}H proline autoradiographic sections 1 μm thick, counterstained with toluidine blue. The photomicrographs are in order of ERM duration (see Table 2). The micrographs do not show representative areas of each ERM but demonstrate the variation in ^{3}H proline uptake between cells (arrows indicate cells incorporating label; arrowheads indicate nuclei of cells).* (a) *Some scattered cells, as evidenced by their nuclei, with background incorporation of ^{3}H proline;* (b) *some scattered cells show pronounced uptake of label;* (c) *two large cuboidal cells incorporating ^{3}H proline surrounded by cells which are not;* (d) *and* (e) *respectively show spindle and cuboidal cells which are so intensely labelled that the nuclei cannot be seen;* (f) *some cuboidal cells show maximal uptake, while others exhibit nearly background levels of incorporation;* (g) *a* late *ERM with a layer of cells in which uptake of label is so intense that individual cell elements cannot be distinguished from each other.* (×*700*).

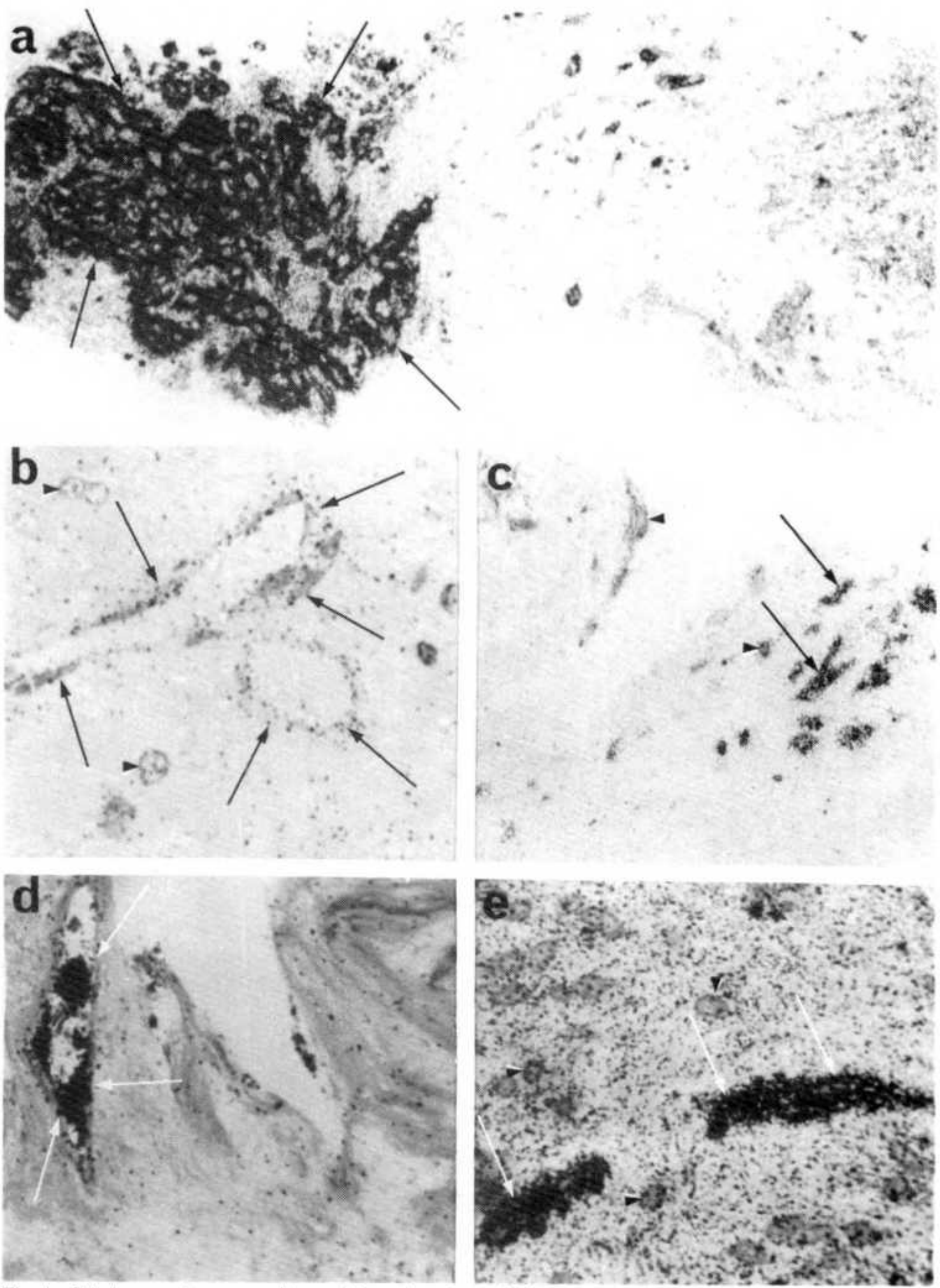

Fig. 4 ^{3}*H glucosamine autoradiographic sections 1 µm thick, counterstained with toluidine blue. The photomicrographs are focused on the silver grains and are in order of ERM duration (see Table 3). The micrographs do not show representative areas of each ERM, but demonstrate that cuboidal cells tend to show more avid label incorporation than spindle cells (arrows indicate cells incorporating label; arrowheads indicate nuclei of cells).* (a) *A coiled layer of cuboidal cells show intense incorporation of label, while spindle cells in the rest of the specimen show background labelling;* (b) *and* (d) *endothelial cells of blood vessels in two ERMs demonstrate weak and intense labelling respectively;* (c) *there is variation from background to moderate* ^{3}*H glucosamine uptake between cell types in this ERM;* (e) *some cuboidal cells show avid* ^{3}*H glucosamine uptake, while others only show background incorporation. (a, c, ×350; b, d, e, ×700).*

Table 4 *Immunohistochemistry of 14 ERMs*

	No.	*Aetiology*	*F/P*	*Actin*			
				Distribution	*Overall staining intensity*	*Intensity in glial aggregates*	*Intensity in epithelial aggregates*
Early epimacular membranes (4)	1	RRD	P	Even	++	NAP	NAP
	2	RRD	P	Even	++	++	NAP
	3	RRD	F	Patchy	++	−	++
	4	RRD	P	Patchy	++	−	NAP
Early MMP membranes (3)	5	RRD	F	Patchy	++	+	+
	6	RRD	P	Patchy	++	NAP	NAP
	7	PT	P	Patchy	++	++	NAP
Late epimacular membranes (4)	8	RRD	P	Even	++	++	+++
	9	RRD	P	Patchy	++	+	++
	10	PT	F	Small foci	++	+	NAP
	11	RS	P	Small foci	+	−	NAP
Late MPP membranes (3)	12	RRD	F	Patchy	++	++	++
	13	RRD	P	Small foci	+	+	+
	14	BT	P	Patchy	++	−	+++

MPP=massive periretinal proliferation. RRD=rhegmatogenous retinal detachment. PT=perforating trauma. BT=blunt trauma. RS=retinoschisis. P=immunoperoxidase technique. F=immunofluorescent technique. NAP=no aggregate present.

foci of cells, but such restrictions of actin staining in *late* ERMs may reflect only a reduced cell population as reported in the quantitative series.

FN staining was intense or moderate overall in all seven *early* ERMs and five out of the seven *late* ERMs (Fig. 5b); the two remaining late ERMs

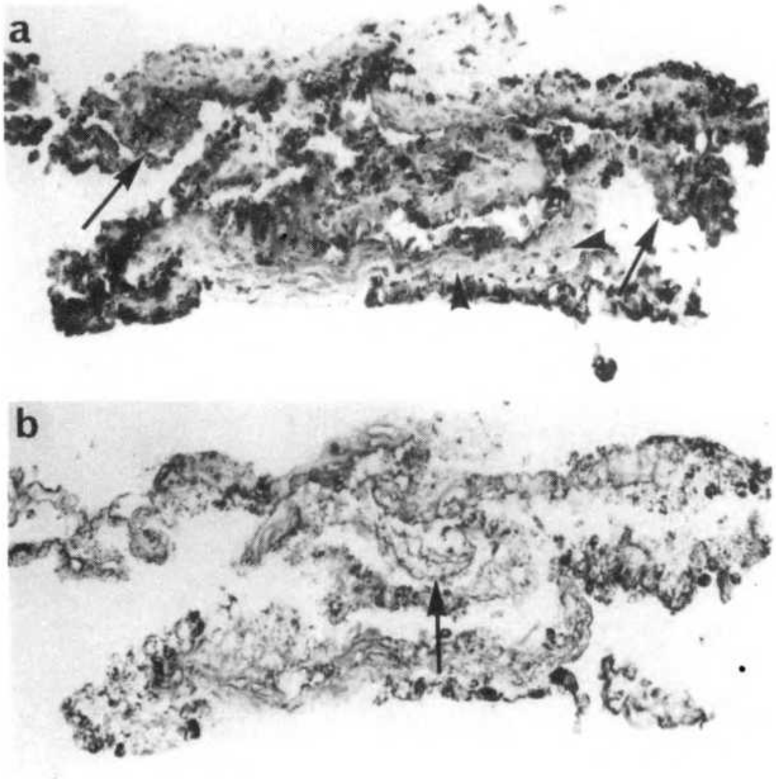

Fig. 5 *Dewaxed sequential 7 μm sections from an early ERM.* (a) *Immunoperoxidase stain for actin shows heterogeneous staining pattern from weak (arrowheads) to intense (arrows), while in* (b) *immunoperoxidase staining for fibronectin shows more homogenous distribution. Note the fibrillar arrangement of fibronectin (arrow).* (×*140*).

	Fibronectin				
Intensity in fibroblast aggregates	*Distribution*	*Overall staining intensity*	*Intensity in glial aggregates*	*Intensity in epithelial aggregates*	*Intensity in fibroblast aggregates*
++	Even	++	NAP	NAP	++
++	Even	++	++	NAP	++
++	Patchy	+++	+++	+++	+++
++	Patchy	++	+	NAP	+++
++	Patchy	+++	+++	+++	+++
++	Even	+++	NAP	NAP	+++
+++	Patchy	+++	+++	NAP	+++
NAP	Patchy	++	++	++	NAP
++	Patchy	++	++	+	++
++	Patchy	+++	+++	NAP	+++
+	Nil	–	–	NAP	–
+++	Patchy	++	++	++	++
++	Patchy	+	+	+	+
+++	Patchy	+++	+	+++	+++

+++ = Intense staining
++ = Moderate staining
+ = Weak staining
– = Background staining

showed nil or weak staining. Both intra- and extracellular FN was stained, and FN staining around clusters of cells was usually more intense than that in hypocellular collagenous areas of ERMs. The distribution of FN in ERMs was usually patchy, but in three *early* ERMs there was a more widespread (even) FN distribution. Thus there was a marginally apparent trend towards more abundant FN staining in *early* than in *late* ERMs, and this reflected the paucity of FN in mature collagen. Strips of inner limiting lamina (ILL), which were present in nine of the 14 ERM specimens, stained weakly for FN (except where the ILL was surmounted by cells, when more intense ILL staining was apparent).

Specific cellular aggregates

Despite some variation of actin staining within individual cell types in ERMs there was a clear-cut difference in actin staining between different cell types (Table 4). Glial cells (Fig. 6a) often stained poorly for actin (Fig. 6b), while fibroblast-like cells stained the most intensely. Epithelial cells, the least represented cell type in the 14 specimens, showed an actin staining level intermediate between glial and fibroblastic cells An exception to this trend was the single ERM with a predominant epithelial component, which showed intense actin staining in some cytokeratin-positive aggregates (Fig. 7a, 7b).

Variable FN staining was seen within clusters of specific cell types, but no obvious trends emerged regarding FN staining intensity between different cell types (Table 4 and Fig 6c).

Discussion

Analyses of precisely aged experimental and human granulation tissue have provided detailed information about the chronological sequence of events in wound healing.[1 4 7 8] We recognise that investigations of postcontractile ERMs removed at inaccurately assessed times during their potentially disparate clinical courses cannot provide equivalent data on the natural history of human epiretinal proliferations. Nevertheless, arbitrary division of a large number of human ERM specimens into *early* and *late* groups (based on clinical history) has revealed trends which indicate that they have certain features in common with the later phase of wound healing. *Late* ERMs, for example, contained fewer cells but more abundant collagen than *early* membranes. The death and disintegration of fibroblasts entombed in collagen thus attests to the ultimate fate of many cells in ERMs, though our reported percentages (25–30%) of necrotic cells may be spuriously high owing to surgical manipulation and removal of the ERMs. Nevertheless, we were impressed by the frequent persistence of layers of glial or epithelial cells adjacent to the fibrous component even in *late* ERMs (reminiscent of the surface epithelium over the healed scar in skin wounds).

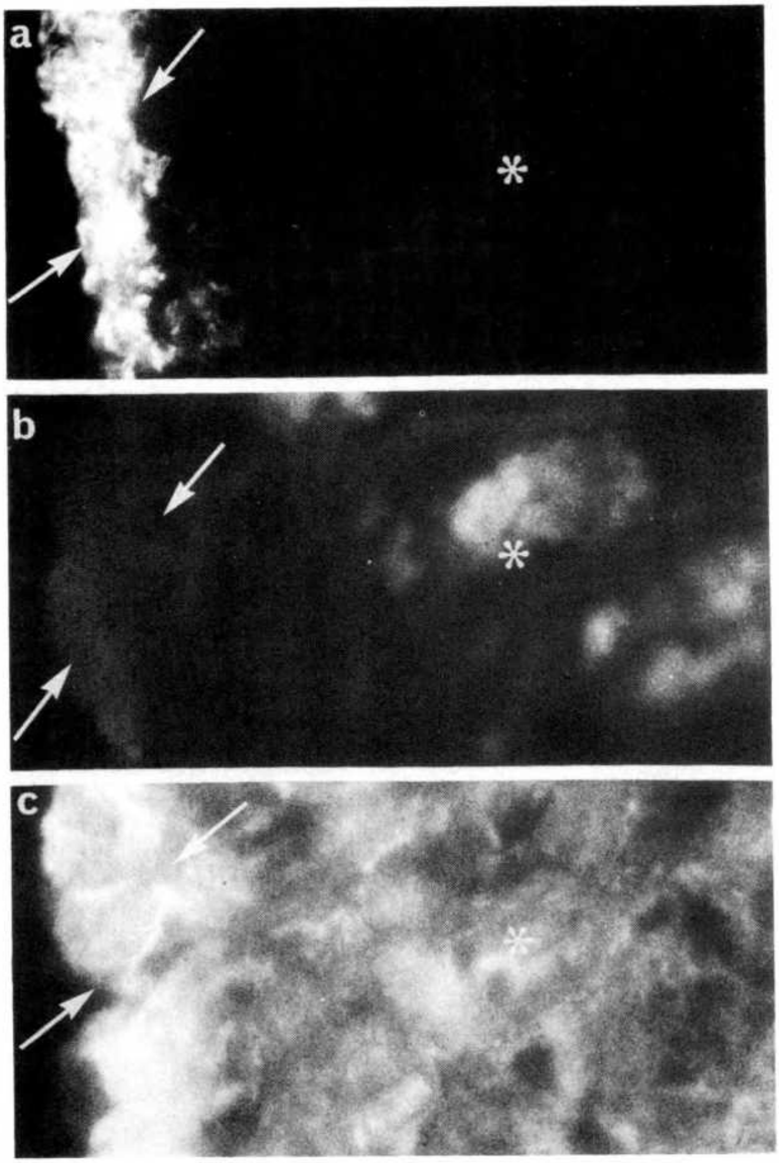

Fig. 6 *Sequential 10 μm frozen sections from an ERM.* (a) *Immunofluorescent stain for GFAP. Note there is a layer of positively staining cells (arrows), which are therefore glial, at the margin of a membrane which contains negative (non-glial) cells (askerisk).* (b) *Immunofluorescent stain for actin. The non-glial fibroblast-like cells stain moderately for actin, while glial cells are only weakly stained.* (c) *Immunofluorescent stain for fibronectin. The glycoprotein can be seen to be present in both glial and non-glial components of the membrane. (×560).*

Trese, Chandler, and Machemer[22] recently reported a clear-cut correlation between the biomicroscopic opacification of ERMs and their collagen content on histopathological analysis. Such a correlation was not confirmed in this study; thin collagenous membranes were often transparent, while essentially cellular ERMs were sometimes opaque (especially those associated with ocular inflammation). This is not surprising when one considers that cellular or subcellular aggregates in an adjacent location to ERMs are also opaque—for example, vitreous snowballs and axoplasmic debris in retinal cotton-wool spots.[23] Thus opacification of a fibrocellular ERM should not necessarily be attributed to its extracellular component; one of several exceptions in our series to the 'opacity means collagen' rule is presented in Fig. 8.

A CONTRACTILE COHESIVE UNIT

During the early stages of wound healing the soluble, dimeric form of FN (derived from plasma and macrophages) stimulates directed migration of fibroblasts towards the wound[24 25]—'chemotactic recruitment'. FN also has a role in cell-to-cell

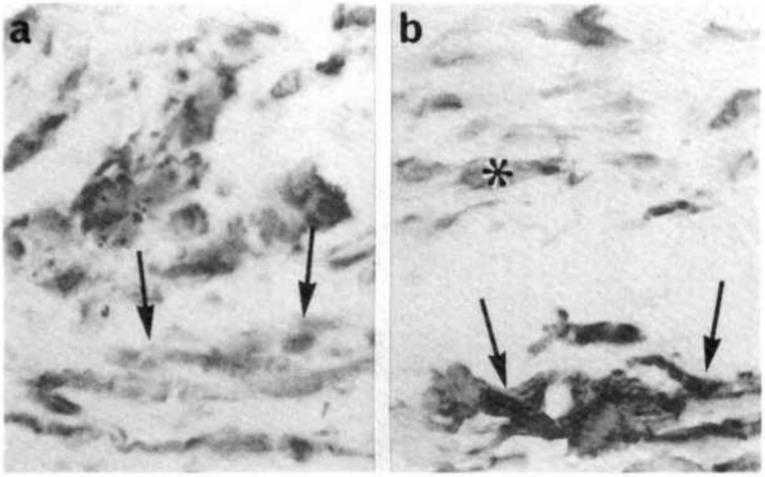

Fig. 7 *Dewaxed 7 µm sections from an ERM containing spindle and cuboidal cells. Arrows show the same area at different depths into the tissue.* (a) *Immunoperoxidase stain for keratin. The cells in the membrane show a positive reaction and are therefore of epithelial origin.* (b) *Immunoperoxidase stain for actin. The epithelial cells show variation in their staining characteristics. Those areas indicated by the asterisk have a moderate reaction, while those arrowed have an intense reaction. (×560).*

adhesion, cell-to-substratum adhesion, and subsequent cell-spreading.[25–27] Thereafter FN is secreted by the fibroblasts themselves (along with procollagen) in an insoluble multimeric form to produce a fibrillar extracellular matrix which has important relationships across cell membranes with microfilament proteins such as actin.[28 29] FN may also enhance phagocytosis of debris in wounds[30] ('opsonic activity') but gradually disappears with maturation of collagen.[3]

FN was abundant in most of the ERMs studied immunohistochemically, being reduced in amount only among dense collagen bundles and being generally deficient in just two very *late* ERMs. The source of FN in ERMs is unclear, although many of the constituent cell types (macrophages, glial cells, epithelial cells, and fibroblasts) are known to be capable of FN synthesis. It is likely that the multiple functions of FN as determined in wounds apply equally well to ERMs—for example, cell adhesion, phagocytosis, and transmembrane relationships with contractile proteins. FN was invarilably present at sites in ERMs where actin staining was prominent. Thus FN appears to be vital not only in stimulating and maintaining the integrity of ERMs but also in linking the contraction of fibroblasts or other actin-containing cells to produce a 'contractile cohesive unit'.

Actin is a component of most ocular cells[31] and is especially prominent during the migratory and contractile phases of experimental vitreous membranes.[32] The relative paucity of intense anti-actin staining in the epiretinal cellular aggregates (and the scarcity of myofibroblasts) may reflect the postcontractile state of the biopsied ERMs. However, the pattern of actin staining in specific cell aggregates was in keeping with the concept that ERM[19 20] contraction is mediated by fibroblasts or epithelial cells (the former being the predominant cell type in most ERMs) and that glial cells do not have a major role in ERM contraction.[19 20]

AN ANARCHISTIC SCAR

Despite the similarities between healing skin wounds and ERMs in terms of component cells and processes there are also striking differences, in particular the duration and sequence of cellular activities. In skin healing the initial cellular proliferation[3] is restricted to a short, clear-cut wave of activity. FN is abundant at first but disappears from experimental dermal scars within five weeks[4] and from corneal wounds within seven days of injury.[33] By contrast our thymidine autoradiographic results suggests that the capacity for cellular proliferation persists well into the postcontractile phase of ERM development, while proline and glucosamine were incorporated into *late* ERMs at levels which compared favourably with those of *early* ERMs. Similarly, FN was abundant in all but the most mature scars. Thus the activities of ERM cells appear to be very protracted, as they are in some visceral wounds,[34] reflecting either unusual persistence of metabolically active subsets of cells or recruitment of additional cells to the ERM during its clinical course. Bearing in mind the absence of any blood supply to most fibrocellular ERMs (which in healing wounds is a key factor in maintaining the activities of cells), the second mechanism (that is, recruitment) appears the more likely, as is further supported by the variation in proline and glucosamine incorporation from cell to cell both within and between cell groups at any given time. Continuing cell recruitment may reflect a persistent stimulus, for example inflammation, and it is of interest that the two eyes in this series showing

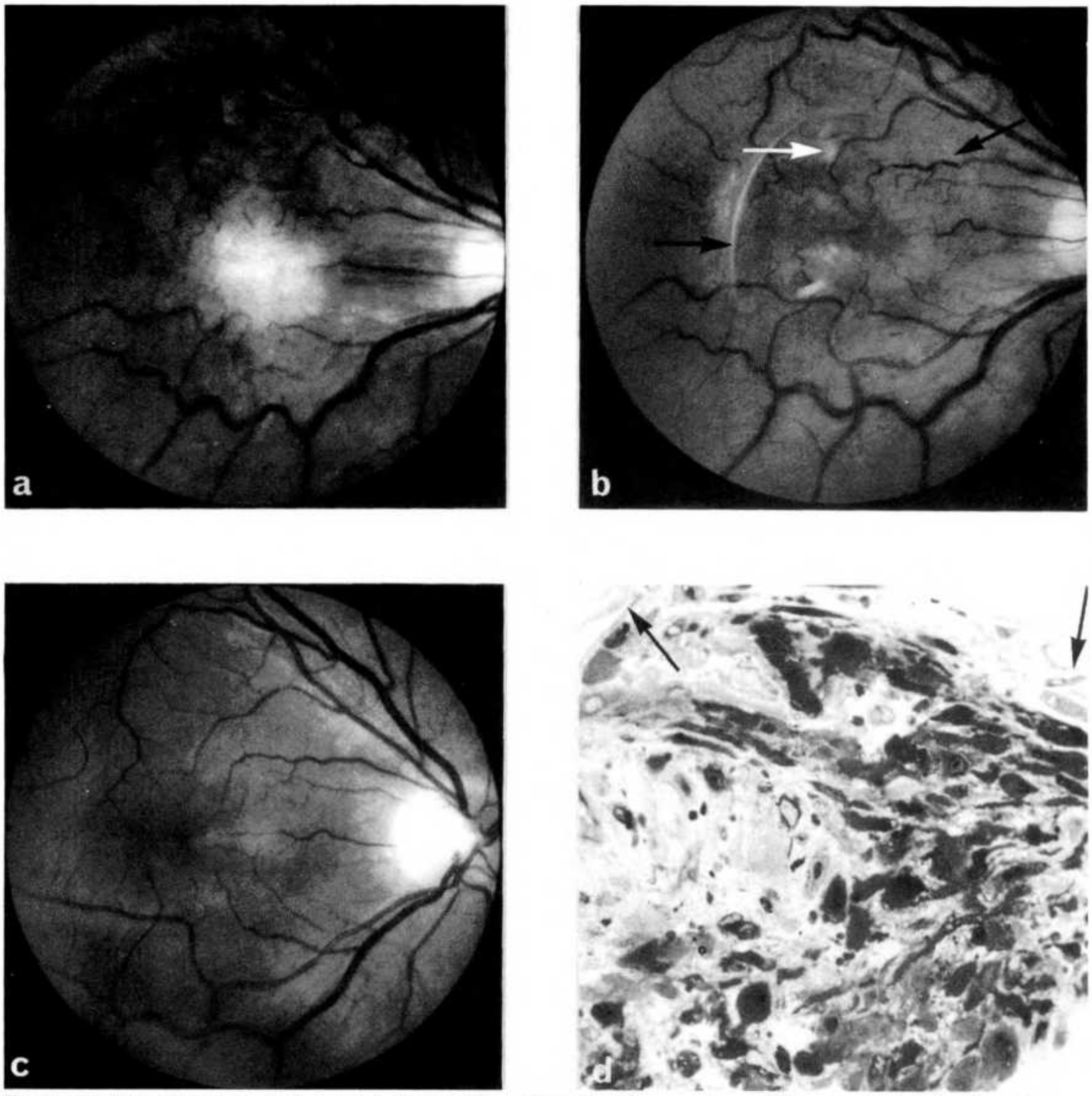

Fig. 8 *Clinicopathological correlation.* (a) *Opaque idiopathic epimacular membrane of three months' clinical duration; outer retinal oedema (arrow) and tortuous vessels (acuity 5/60).* (b) *Three days after membrane dissection; circular edge of excised cortical gel and ILL (black arrows) and axoplasmic debris (white arrow).* (c) *Four months after membrane dissection; spontaneous detachment of residual gel and ILL, and restoration of course of major vessels (acuity 6/6).* (d) *Light microscopy of ERM specimen showing heterogeneous hypercellular membrane with bizarre cell forms attached to ILL (arrows); minimal collagen content.* (×250).

recurrent proliferation after epimacular membrane peeling had pars planitis.

What are the implications for treatment of these poorly regimented (or 'anarchistic') activities of ERMs as revealed in organ culture? Certainly persistent recruitment of cells into ERMs poses considerable problems in planning treatment regimens by antiproliferative agents such as 5-fluorouracil. By contrast the disorderly behaviour of ERM cells probably underlies the abundance of FN seen at all stages of ERM development. Since experimental studies have shown that some of the effects mediated by this glycoprotein can be blocked,[24-26] FN might represent a more opportune target at which drug or immune intervention could be aimed in the management of ERMs.

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British Journal of Ophthalmology, 1985, **69**, 824–826

Variability of the hill of vision and its significance in automated perimetry*

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SUMMARY It has been assumed that the retinal threshold sensitivity profile is a standard which decreases predictably with age. On this basis the significance of relative scotomata is decided on certain types of perimeter. The hill of vision was measured in 128 healthy eyes on the Dicon 2000 autoperimeter. We found a large variation between individuals, with no relationship to age. The relevance of the findings to automated perimetry are discussed.

Automated static perimeters screen the visual field at selected points. They may establish the threshold sensitivity at each point and compare it to an assumed age related value, as is the case with the Octopus.[1] Otherwise a stimulus greater than the assumed normal threshold value is used on the premise that any missed point shows a significant defect. The suprathreshold technique developed by Armaly[2] on the Goldmann perimeter, and later modified,[3] has the advantages of speed and reproducibility in the hands of different operators.[4] It is used on many automated perimeters, including the Fieldmaster,[5] the Friedmann,[6] and the Dicon. The Fieldmaster uses two levels of suprathreshold stimulus, the stronger one beyond 30° of eccentricity. In the case of the Friedmann the threshold is not assumed but is determined for each patient; however, the shape of the hill of vision is assumed.

The Dicon perimeter measures the individual profile by simultaneous stimulation in four quadrants at equal eccentricity under photopic conditions. This circumvents possible error due to local field defects. Glaucoma screening is then performed at 0·4 log unit (LU) suprathreshold. We discuss the measurements from 128 such hills of vision and their implications on automated perimetry.

Materials and methods

The hill of vision was measured on the Dicon 2000 automated perimeter with a background illumination of 31·5 apostilbs (Asb) and a spot size Goldmann II. Threshold was determined by simultaneous stimulation in four quadrants along the 45°, 135°, 225°, and 315° meridians at equal eccentricities of 2·5°, 5°, 15°, 25°, 40°, and 60°. A semibracketing technique is used where alternative stimulation above and below threshold in decreasing steps is concluded by a double confirmation to a resolution of 0·2 LU.

Our 128 subjects were drawn from members of staff at the Manchester Royal Eye Hospital and patients attending its Accident and Emergency Department with a visual acuity of at least 6/12 in their healthy (tested) eye. Of these subjects 60 were grouped according to age (Table 1). One eye per subject was tested, with a reading correction when applicable.

Results

The hill of vision may be described in three parts: the central peak, the mid-plateau from 15° to 25° eccentricity, and the peripheral decline. The components of 128 hills of vision were analysed with reference to the central peak height, the threshold sensitivity of the mid-plateau, and the degree of peripheral decline (Fig. 1).

Table 1 *Description of age groups*

Group	*Age range (years)*	*Visual acuity range*	*Number of subjects*
I	9–29	6/5–6/6	20
II	30–49	6/5–6/9	20
III	50–80	6/5–6/12	20

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*This paper was given under another title and in a different form at the 6th International Perimetric Symposium in Genoa on 27–31 May 1984

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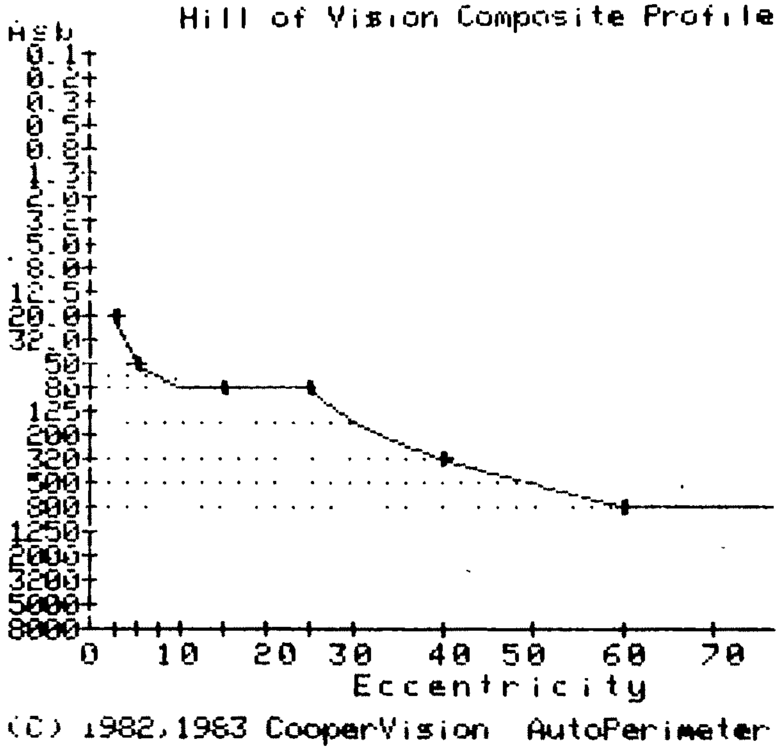

Fig 1 *A typical hill of vision described in three parts: the central peak, the mid-plateau from 15° to 25°, and the peripheral decline.*

The central peak height (Fig. 2). Its height was taken from the level of the mid-plateau at 15° eccentricity, and it showed a flat distribution over a range of 0 to 1·0 LU. The largest group of 43% was found at 0·2 LU.

The mid-plateau threshold sensitivity (Fig. 3). For this measurement we used the sensitivity at 15° in all cases. Although 37·5% of plateaus were sloping, only two fell by more than 0·4 LU. The plateau sensitivity was concentrated, giving a sharp distribution with 89% of values found in the 50 and 80 Asb groups.

The degree of peripheral decline (Fig. 4). The drop in sensitivity from 25° skewed to the left over the range 0 to 1·8 LU. Although the first group (0 to 0·4 LU) was the largest at 57%, 13% of declines were greater than 1·4 LU. Only four subjects showed no decline.

The relevance of age to the hill of vision was assessed by comparing three groups (Table 1). The average peak height for each group was found to be

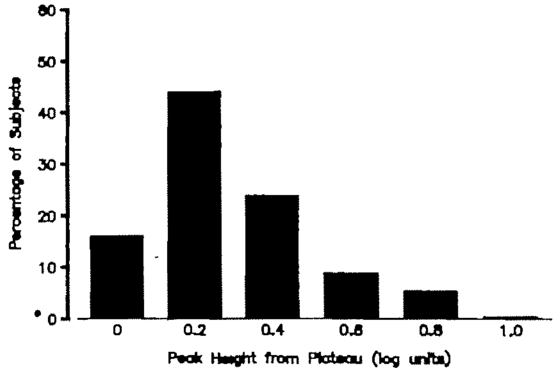

Fig. 2 *The central peak· distribution according to height in 128 subjects*

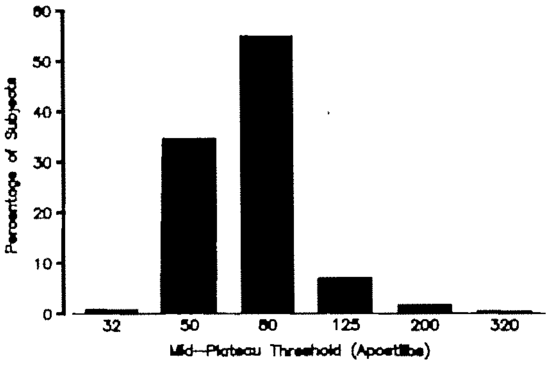

Fig. 3 *The mid-plateau: distribution according to threshold sensitivity in 128 subjects.*

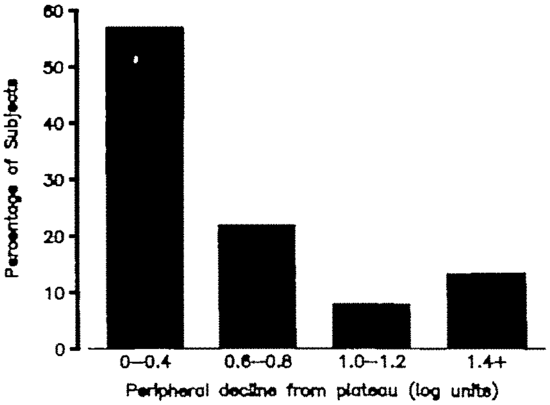

Fig. 4 *The peripheral decline: distribution according to degree of fall in 128 subjects.*

highest in group II and lowest in group III (Table 2). Looking at the mean value of the mid-plateau threshold for each group, taken between the 15° and 25° sensitivities, we found no significant difference between groups. The highest value was found in group III. However, variation within groups showed a decrease with age.

Discussion

In deciding the significance of relative scotomata many automated perimeters must refer to standard values of threshold sensitivity and characteristics of profile deemed normal. Our findings show surprisingly large differences in both these respects among individual hills of vision. Both the central peak height and the degree of peripheral decline varied markedly (Figs. 2, 4). Although the mid-plateau sensitivities showed less variation (Fig. 3), it was significant, especially in view of the fact that 37·5% of plateaus were sloping. The results of subjects grouped by age (Table 2) failed to demonstrate any loss of sensitivity with increasing age One subject aged 80 had a mid-plateau threshold of 50 Asb, whereas another aged 9 had one of 65 Asb

Table 2 *The central peak height and mid-plateau threshold: correlation with age*

Group	*Average central peak height from plateau (log units)*	*Average mid-plateau threshold with standard deviation (Asb)*
I	0 38	67 9±18
II	0 43	66·0±14
III	0·28	70·2±12·8

The concept of a hill of vision of uniform profile which decreases in sensitivity with increasing age is erroneous. Accurate perimetry depends on combining a high sensitivity (minimal false negatives) with a high specificity (minimal false positives). Variation from an assumed 'normal' in threshold related testing will give reduced specificity where threshold is above that expected and reduced sensitivity where it is below. In suprathreshold testing, which assumes a 'normal', the degree of suprathresholdness can be increased to maintain specificity at the cost of reducing sensitivity.

By tailoring the suprathreshold stimuli to the individual hill of vision it should be possible to maintain a high specificity with a minimal degree of suprathresholdness and hence a minimal loss of sensitivity.

We extend our thanks to Lynn Griffin for her secretarial assistance and to the Departments of Medical Illustration at the Manchester Royal Infirmary and at the Manchester Medical School.

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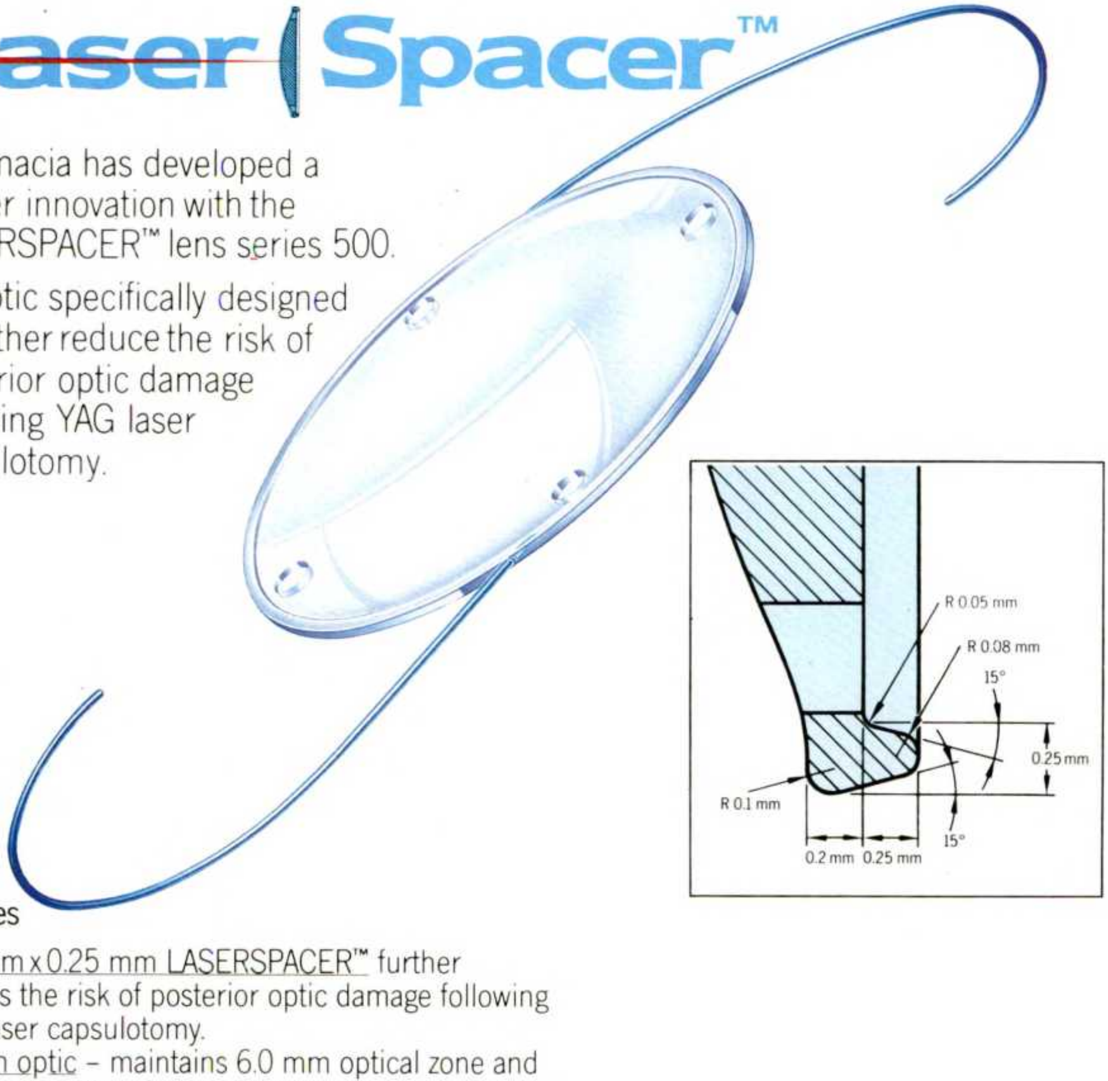

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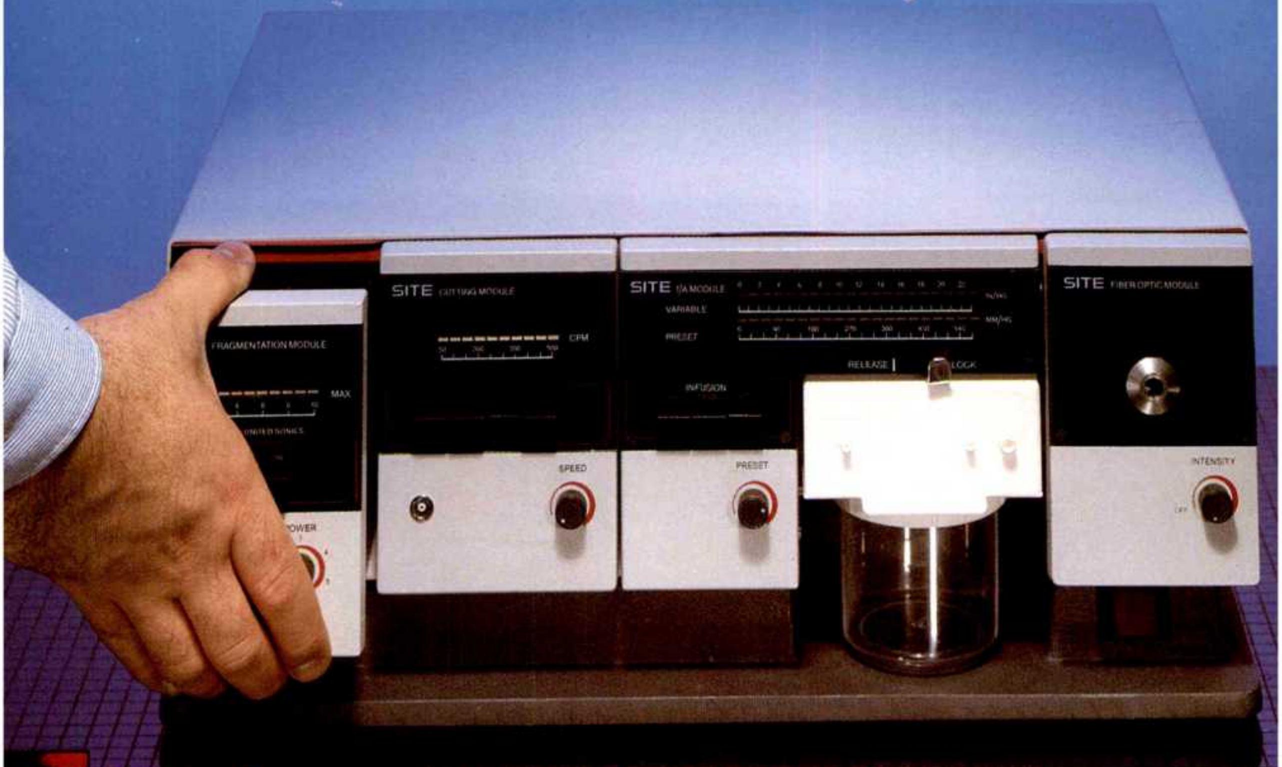

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Progression of field loss after trabeculectomy: a five-year follow-up

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SUMMARY We report a retrospective study of 60 eyes from 46 patients all with primary open-angle glaucoma who had a trabeculectomy to one or both eyes. A minimum five-year follow-up was available. The percentage pressure reductions at the one and five years postoperatively is shown. In a subgroup of 50 eyes which had Goldmann fields documented at least six-monthly for a minimum of five years postoperatively there was a continuation of glaucomatous field loss in 18% of eyes despite postoperative pressures in the normal range. The five-year percentage pressure reduction and the minimum percentage pressure reductions were statistically significant in a comparison between the field loss and no field loss groups. However, in the individual case there seemed no way of predicting which eyes would develop postoperative field loss, and regular postoperative perimetric assessment was found to be essential whatever the pressure measurements recorded.

Trabeculectomy is now generally considered to be a useful and relatively safe procedure in the management of chronic open-angle glaucoma. There is a trend towards earlier surgical intervention in the disease without necessarily establishing failure of 'maximum' medical therapy but proceeding instead to surgery if one or two medical regimens fail to reduce the pressure to satisfactory levels. Watson and Grierson[1] and others have stated that early surgical intervention in most cases is desirable and that long-term topical treatment has undesirable side effects (particularly with those agents causing an under-perfusion of the meshwork). However, we emphasise that despite apparently good postoperative control, in some patients, field loss continues to occur. Although there are many reports of the results of trabeculectomy and other pressure-lowering operations,[2-5] relatively few of them report on a minimum five-year follow-up, particularly with regard to continued field loss.

Subjects and methods

This retrospective study included 46 patients, 16 male and 30 female, aged between 39 and 79 years at the time of surgery, with a mean age of 61 years. All patients were diagnosed as having primary open-angle glaucoma on the basis of raised intraocular pressures (greater than 21 mmHg), glaucomatous field defects, and open angles.

The intraocular pressure in a total of 60 eyes from the 46 patients was uncontrolled on maximum medical therapy (two topical agents plus or minus a carbonic anhydrase inhibitor).

The 60 eyes included in the study had had only one drainage procedure (trabeculectomy) and were followed up for a minimum of five years postoperatively. In all cases the standard Watson modification[6] of the Cairns procedure[7] was performed.

All the patients were followed up at the Glaucoma Unit of the Belfast City Hospital. In 50 of the eyes Goldmann perimetry was performed at six-monthly intervals from between six months and six years preoperatively and at least six-monthly intervals postoperatively for a minimum of five years. All fields were tested by the same associate specialist at the unit. The field charts were examined by one of us (MNK) in a manner ensuring that the date of the operation was unknown. Progression of glaucomatous field loss was judged to have occurred when one or more of the following criteria[4] were met: (1) widening of a nasal step or other field defect by 5° or more; (2) the appearance of a new scotomatous defect; (3) a change for relative to absolute scotoma.

Intraocular pressures were estimated by applanation tonometry. The mean of the preoperative read-

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Table 1 *Intraocular pressures with and without treatment (TR) at the end of the one- and five-year postoperative periods*

Pressure	*1 Year postop*		*5 Years postop*	
	No	*%*	*No*	*%*
<21 (No TR)	52	86 6	45	75·0
<21 (With TR)	2	3 33	12	20·0
>21 (With TR)	6	10·0	3	5 0

ings for each eye was noted, as were the mean values of the intraocular pressures taken during the one- to five-year postoperative periods.

Data on the eyes from the groups with and without field loss were subjected to statistical analysis. The data were non-parametric, and the Mann-Whitney test was used throughout.

Results

Forty-five eyes (75%) required no postoperative medication throughout the study period. Fifty-two eyes were receiving no medication at the end of the first postoperative year, and, of these, seven (13·46%) required medication at the end of the five-year period (Table 1). The mean preoperative intraocular pressure of the 60 eyes was 25·1 mmHg. The mean postoperative intraocular pressure at the first visit was 13·04 mmHg. The mean of all the postoperative intraocular pressures at the end of the first year (with or without treatment) was 13·76 mmHg, and the mean of the postoperative intraocular pressures at the end of five years (with or without treatment) was 14·95 mmHg.

Table 1 shows that six eyes had a pressure in excess

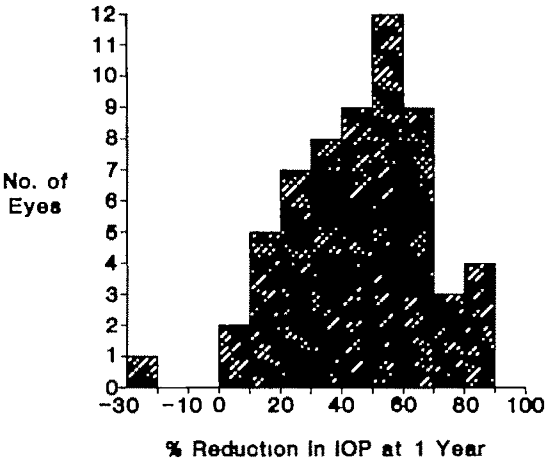

Fig. 1a *Percentage reduction in IOP at end of one-year period.*

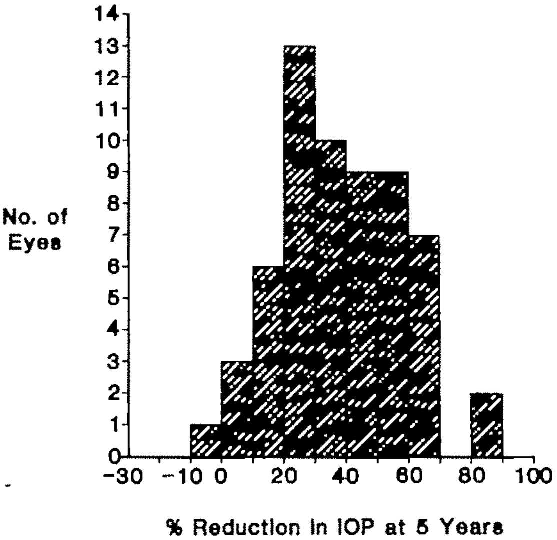

Fig. 1b *Percentage reduction in IOP at end of five-year period.*

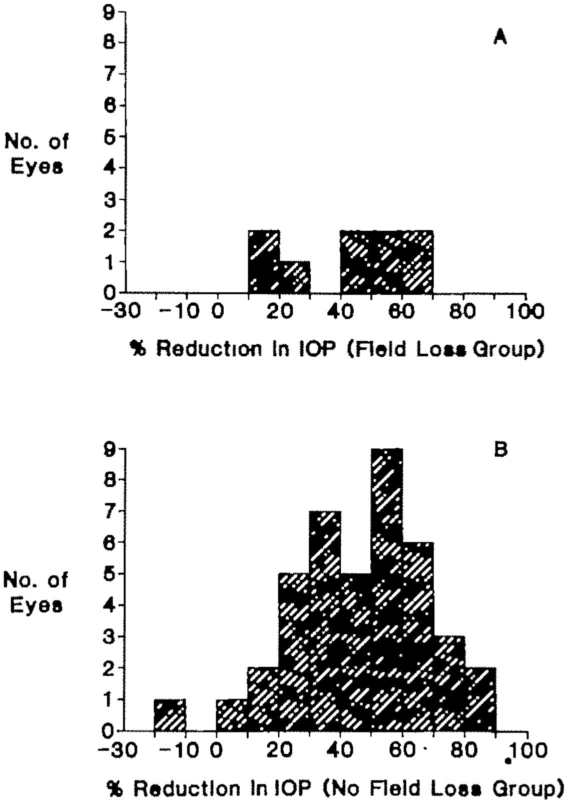

Fig 2 *Percentage reduction in IOP at end of one-year postoperative period for the 'field loss' (A) and 'no field loss' (B) groups*

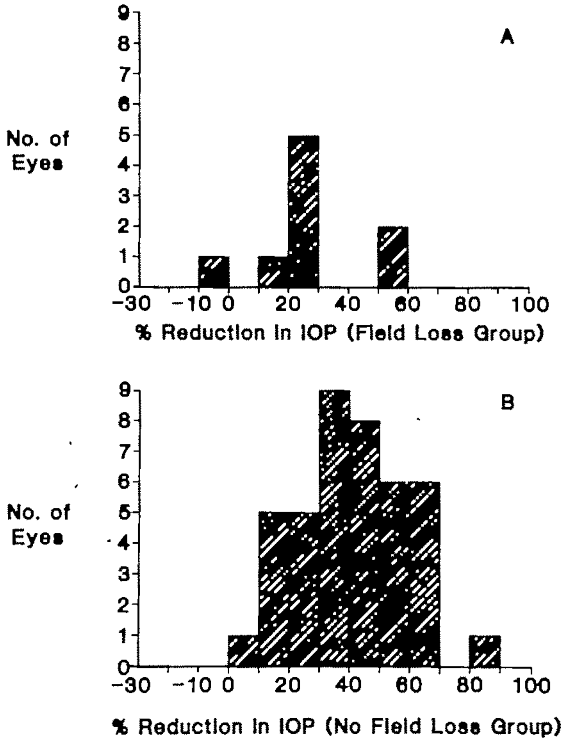

Fig. 3 *Percentage reduction in IOP at end of five-year postoperative period for the 'field loss'* (A) *and 'no field loss'* (B) *groups.*

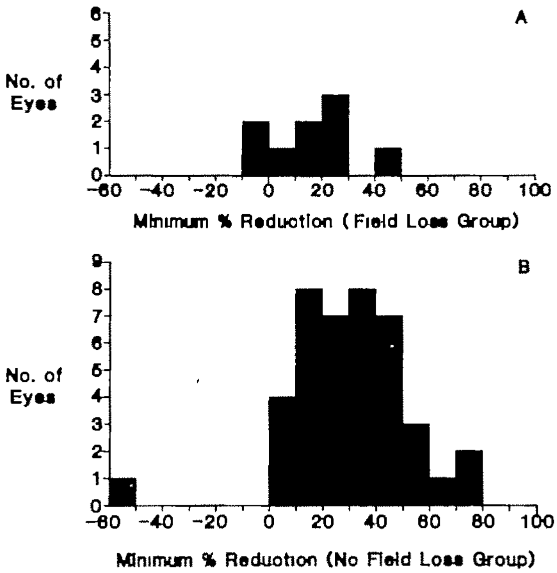

Fig. 4 *Minimum percentage reduction in IOP throughout the study period for the 'field loss'* (A) *and 'no field loss'* (B) *groups*

of 21 mmHg with medication at the end of the first postoperative year, and the figure for this category at the end of the five-year period was three eyes. Three eyes had additional medical therapy which brought them down to less than 21 mmHg.

Figs. 1a and 1b show histogramatically the percentage pressure reduction at the end of the one- and five-year periods of study with or without therapy. There was a slight trend towards less reduction in pressure when the one- and five-year periods are compared. The mean of the percentage reduction in pressure at the end of the one-year period was 45·26%, and the mean percentage reduction at the end of the five-year period was 39·23%.

In the subgroup of 50 eyes for which field documentation over the period of study was available nine (18·0%) had glaucomatous field loss at the end of the fifth postoperative year. Figs. 2 and 3 show the percentage pressure reductions at one and five years respectively for the 'progression of field loss' and 'no progression of field loss' groups.

Fig. 4 shows the minimum percentage pressure reductions in the 'progression of field loss' and 'no progression of field loss' groups. This is calculated from the highest recorded postoperative intraocular pressure reading.

Although a trend is seen towards less percentage pressure reduction (Table 2) at the end of the first

Table 2 *The various mean values for the 'field loss' and 'no field loss' groups, showing the significant values*

	Progression of field loss group	*No progression of field loss group*	*p*
No. of eyes	9	41	
Percentage	18·0	82·0	
Mean preop IOP	23·66	24·78	0·13
Mean 1 year postop IOP	14·22	13·92	0·48
Mean 5 years postop IOP	17·33	14·92	0·06
Mean of minimum % reduction	15·56	29·72	0·03*
Mean 1 year % reduction	34·5	44·2	0·48
Mean 5 years % reduction	26·6	40·34	0·03*
Mean of age at date of op. (years)	62·1	61·1	

*Significant at 5% level

year postoperatively between the two field groups, it was only at the end of the five-year period that the trend is significant. The mean of the minimum percentage pressure reduction in the two groups is significant at the 5% level.

Fig. 5 shows the immediate preoperative and four-year postoperative Goldmann fields of a female patient of 58 years at the time of surgery. Her recorded postoperative pressures were never above 17 mmHg. It can be seen that glaucomatous field loss progressed.

Fig. 6 is another example of a patient in the 'progression of field loss' group. This female was 61 years of age at the time of surgery. Her postoperative pressures were never recorded above 12 mmHg. The figure shows progression of the field when the one-year and four-year postoperative fields are compared. No preoperative disc photographs were available for study when comparing the 'progression of field loss' and 'no progression of field loss' groups, but on examining the presurgical fields from the two groups we found a similar distribution in each group of early, moderate, and late glaucomatous field loss according to the criteria outlined.

Only two of the nine eyes in the 'progression of field loss' group had extensive initial field loss. The other seven showed early field loss represented by only a small arcuate scotoma. Fig. 6 is typical. It was decided to ignore other observers' comments in the medical charts on the state of optic disc cupping.

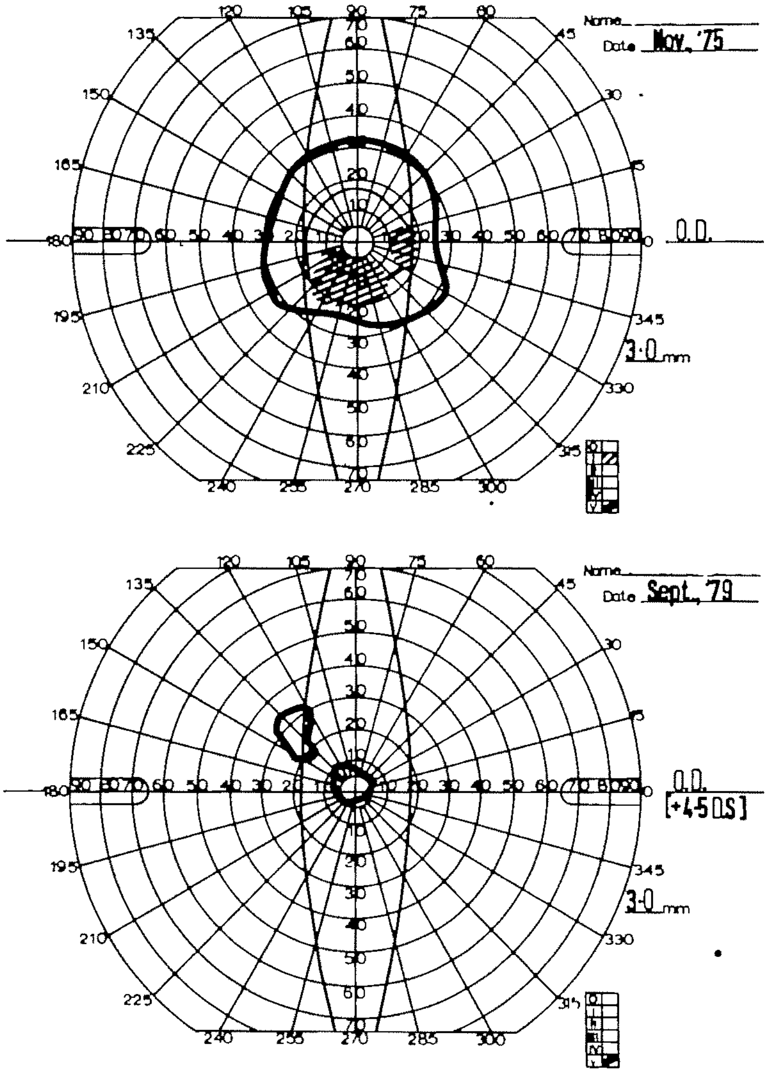

Fig. 5 *Immediate preoperative and four-year postoperative Goldmann fields of a patient in the 'field loss' group (see text).*

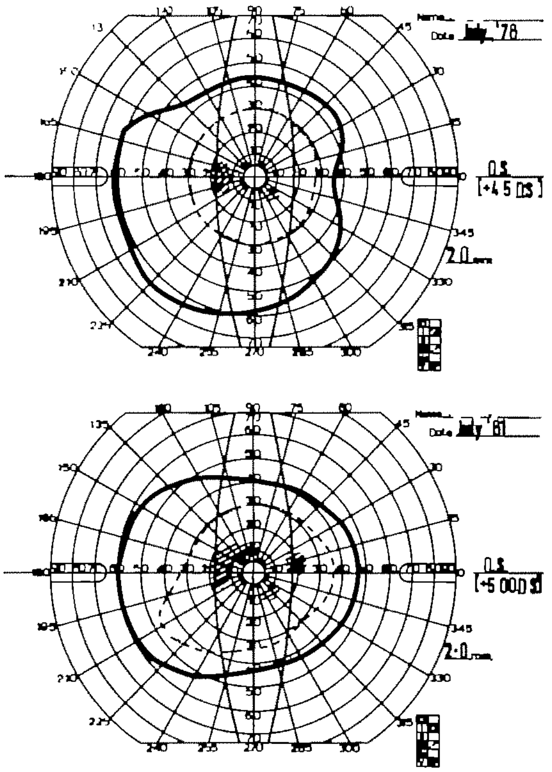

Fig 6 *One- and four-year postoperative Goldmann fields of a patient in the 'field loss' group (see text).*

Discussion

Although it is becoming increasingly apparent that there is no simple correlation between raised intraocular pressure and progression of field loss and that other factors may play a part, it is still common practice to consider chronic open-angle glaucoma 'cured' when postoperative intraocular pressures remain within normal limits.

Other factors which may be important are age, generalised microvascular disease, systemic hypertension, and genetic factors.

In this study we noted that nine out of 50 eyes (18%) continued to lose field postoperatively despite satisfactory pressure measurements. Rollins and Drance[4] cite a figure of 29% progression of field loss despite pressure measurements postoperatively in the normal range.

Although the mean one- and five-year postoperative readings of intraocular pressure for the 'no progression of field loss' group were less than those of the 'progression of field loss' group, the difference was not significant at the 5% level. Statistical significance was found, however, at this level for the mean of the minimum percentage reduction for the 'progression of field loss' and 'no progression of field loss' groups. This indicates that in the 'no progression of field loss' group there was less variation in individual pressure measurements.

In addition the difference in the mean five-year percentage reduction in intraocular pressures between the two groups was significant at the 5% level. Although a similar trend is shown at the end of one year after operation, it was not shown to be significant

The results are in agreement with the findings of others[4,5] in showing that the reduction of the intraocular pressure by surgical means does not necessarily protect the eye from further field loss. Surgery, however, may reduce the rate of field loss in every patient. Although we did not have accurate documentation of disc changes in our patients, we recognise the susceptibility of the severely cupped disc to nerve fibre loss at normal intraocular pressures. However, we noted that the distribution of early, moderate, and late field loss, and therefore presumably related nerve fibre loss, was similar in the groups under consideration.

The difference between the two field groups in the minimum percentage reduction and the five-year percentage reduction in intraocular pressure was statistically significant, but in the individual patient's case there seems no way of forseeing this, and we emphasise the need for regular perimetry after trabeculectomy regardless of the intraocular measurements. If further field loss is noted, accurate phasing should be undertaken and consideration given to a further reduction in the IOP by medical means.

Grateful thanks are extended to Dr Doreen Linton of the Glaucoma Unit, who performed the perimetry in the study

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Patterns of lacrimal dysfunction in primary biliary cirrhosis

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SUMMARY The lacrimal function has been evaluated in 23 patients suffering from primary biliary cirrhosis by rose bengal test, the Schirmer test 1, and the tear breakup time. Ocular dryness was present in 78% of cases studied. No difference was found with respect to the length or severity of the hepatic involvement between patients with and without lacrimal dysfunction, but in patients with signs of hypolacrimation the changes in the lacrimal tests increased with the duration and histological progression of liver disease.

Primary biliary cirrhosis (PBC) is a chronic cholestatic disease. It is characterised by granulomatous infiltration of portal tracts with destruction of intrahepatic bile ducts.[1] It is associated with a variety of immunological abnormalities. Among them are a close association with M2-antimitochondrial antibodies,[2] found in nearly 90% of cases, alterations of cell mediated immune functions, and increased serum IgM immunoglobulins.[3] Recently an aberrant expression of HLA-DR antigens on bile duct epithelium has been demonstrated.[4] Besides the biliary ducts the lacrimal, salivary, and pancreatic ducts may also be involved, thus presenting the picture of a 'dry gland syndrome'.[5] PBC should therefore be regarded as a systemic disease rather than a disorder confined to the liver. The involvement of different organs may induce a variety of clinical pictures, whose common denominator is the presence of chronic liver disease.

The frequent occurrence of ocular dryness[4-9] has led us to study the presence of possible correlation between lacrimal dysfunction and the histopathological stage, serological parameters, and duration of liver disease.

Material and methods

Twenty-three patients (21 females) ranging in age from 42 to 75 years were studied. The disease duration varied from 1 to 15 years. The patients showed typical biochemical changes (Table 1); all of them were positive for antimitochondrial antibodies (AMA) and had a liver histology (biopsy and/or laparoscopy) supporting the diagnosis of PBC.

The patients had no significant eye disorders other than eye dryness, and on the basis of the American Rheumatism Association criteria none of them had osteoarticular symptoms or signs suggesting the diagnosis of rheumatoid arthritis.

The liver biopsy findings were classified in four stages according to accepted criteria.[10]

The ophthalmological investigations included the following,

(1) A history with particular emphasis on conjunctival-lacrimal symptoms.

(2) Biomicroscopic analysis of the anterior and posterior segments.

(3) Tear breakup time (BUT): values lower than 10 seconds are generally considered suggestive of an early rupture of the precorneal film.[11]

(4) Rose bengal test. We referred to Van Bijsterveld's classification[12] to assess the severity of the corneoconjunctival epitheliopathy (four stages with increasing severity: degree 0=no impregnation, degree 1=low impregnation, degree 2=medium impregnation, degree 3=high impregnation) and to indicate the site (arabic numerals 1, 2, and 3) for temporal bulbar conjunctival, nasal bulbar conjunctival, and corneal, respectively. The rose bengal test was considered positive when a degree 1 epitheliopathy was present in at least two corneocon-

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Table 1 *Biochemical parameters of 23 PBC patients*

Case	*TB*	*AP*	*Chol*	*Alb*	*Glob*	*IgG*	*IgA*	*IgM*	*AMA titre*
1	0 25	82	270	3·6	1·7	1436	205	557	1·320
2	0 4	75	268	4·2	1·9	1735	511	560	1 320
3	5	330	281	4 00	2·6	2166	493	1079	1.320
4	0·4	210	175	3 7	1·3	1200	250	160	1:320
5	1·4	163	467	4·1	1·5	1007	160	452	1 40
6	0·6	75	269	4·00	1·1	640	212	562	1 320
7	0·5	58	150	4·5	1 3	1058	398	680	1 80
8	1·5	90	220	2·8	1·9	1500	215	160	1:80
9	1 2	70	183	4·35	2·2	2350	780	380	1:320
10	19·8	120	128	2·4	2·8	1970	1180	544	1:160
11	1 4	175	233	4·1	1·8	1644	402	586	1 320
12	6·5	40	180	2·4	1·8	1740	500	560	1 80
13	2·6	115	154	2 5	3·4	2750	775	1940	1·320
14	0·5	13	214	4·4	1·0	1220	79	410	1 80
15	1 0	112	307	4·2	2 4	3200	812	680	1.320
16	1 6	27	158	2·7	3 2	2640	729	520	1:80
17	1·6	27	158	2·7	3·2	2644	729	520	1:80
18	0·85	177	210	2·6	2·9	2800	450	230	1 80
19	0 35	106	240	3·2	2·3	1365	440	1486	1.160
20	0·45	115	270	4 00	1·4	1250	100	440	1:10
21	0·5	89	200	4·2	1·6	1224	232	764	1.320
22	8·1	185	289	4·5	1 1	1270	560	335	1.320
23	0·6	35	249	4·5	1·7	1330	274	1248	1:20

TB = total bilirubin (normal 1 mg/dl) AP = alkaline phosphatase (normal 12–30 mU/ml). Chol = cholesterol (normal 150–250 mg/dl)
Alb = albumin (normal 3·6–4·3 g/dl). Glob = gammaglobulins (normal 1·1–1·4 g/dl). IgG normal range = 420–1450 mg/dl
IgA normal range = 60–480 mg/dl. IgM normal range = 50–390 mg/dl
SI conversion TB mg/dl × 17·1 = μmol/l Chol mg/dl × 0·0259 = mol/l Alb and Glob g/dl × 10 = g/l. Ig mg/dl × mg/l.

junctival zones. The data reported in Table 2 represent the mean value of the two eyes.

Tests 3 and 4 are not affected by the age of the patients.

(5) Schirmer's tests 1. Each patients was tested by using blotting paper strips 5 mm wide and 55 mm long (blue Carlo Erba litmus paper) inserted 5 mm down from the temporal side of the inferior fornix. The test

Table 2 *Relation between clinical data and lacrimal function in 23 PBC patients*

Case	*Age*	*Sex*	*Stage*	*Duration (years)*	*Eye symptoms*	*Rose bengal*	*Schirmer 1 (normal ≥10 mm)*	*BUT (normal ≥10 s)*
1	63	M	I–II	1	–	$1_1 2_1 3_0$	9–11	25–30
2	54	F	I	2	+	$1_1 2_1 3_0$	11–12	10–10
3	48	F	I	3	–	$1_1 2_1 3_0$	9–9	10–11
4	60	M	I	3	+	$1_1 2_1 3_0$	6–10	20–20
5	47	F	II	3	–	$1_1 2_1 3_1$	9–9	12–12
6	52	F	II	3	+	$1_1 2_1 3_0$	5–5	11–12
7	69	F	I–II	6	+	$1_1 2_0 3_0$	9–10	5–8
8	51	F	III	3	+	$1_1 2_2 3_1$	16–15	6–8
9	66	F	III	7	+	$1_1 2_1 3_0$	9–11	16–16
10	55	F	IV	8	+	$1_0 2_2 3_1$	12–6	8–7
11	47	F	III–IV	9	–	$1_1 2_1 3_1$	2–2	7–8
12	52	F	IV	10	+	$1_1 2_2 3_0$	3–6	9–8
13	63	F	IV	12	+	$1_2 2_2 3_1$	1–2	5–6
14	59	F	III–IV	8	+	$1_2 2_2 3_2$	3–3	5–6
15	75	F	IV	13	+	$1_2 2_2 3_2$	1–3	7–8
16	68	F	IV	13	–	$1_1 2_1 3_1$	7–7	9–9
17	71	F	IV	14	–	$1_1 2_2 3_1$	9–9	9–7
18	42	F	IV	15	+	$1_2 2_2 3_3$	6–9	7–7
19*	50	F	I	2	–	$1_1 2_0 3_0$	15–17	20–20
20	49	F	I	4	–	$1_0 2_0 3_0$	10–16	15–15
21	57	F	III–IV	3	–	$1_0 2_0 3_0$	10–16	14–20
22	72	F	III–IV	4	–	$1_0 2_0 3_0$	15–16	20–20
23	58	F	IV	7	–	$1_0 2_0 3_0$	15–20	12–13

was performed with open lids, with the patients' eyes turned upwards. As Schirmer's test 1 is affected by age[13-15] in subjects under 60 years, only values lower than 10 mm after 5 minutes were regarded as suggestive of hypolacrimation.

Results

The results in each patient are reported in Table 2, as well as age, histological stage, duration (in years) of the disease, and the presence of ocular symptoms suggestive of eye dryness.

Twelve patients (52%) had symptoms of ocular dryness, all of them lacrimal dysfunction. Functional changes without symptoms were observed in a further six patients. Thus 18 patients (78%) gave abnormal results in the lacrimal tests. In particular the rose bengal test was positive in 17 cases (74%), the Schirmer's test in 12 (52%), and the BUT was reduced in 11 (48%). The results of the Schirmer's test 1 in cases 1, 7, 9, 17, were not regarded as positive because of the age of the patients (63, 69, 66, 71 years respectively).

As to the relation between the results of lacrimal tests and liver histology, Table 2 shows that simultaneous positive results of the three lacrimal tests were never found in 9 patients with stages I and II PBC, and two early cases had a normal lacrimal function. Simultaneous positive results of the three tests were found in eight out of 14 patients with stages III–IV PBC, while three patients showed no eye disorder at all.

No correlation between AMA titre, serum IgM levels, and the presence or degree of ocular dryness was found.

The relation between lacrimal function tests and the duration of disease in the 15 patients with altered lacrimal function is shown in Table 2. The rose bengal test was clearly the first to be altered, followed by Schirmer's test 1 and the BUT test. In eight of the nine stage III-IV PBC patients with a duration of disease of 8–15 years all the tests were simultaneously altered

Discussion

As was expected, lacrimal function tests are more sensitive than ocular symptoms in the detection of lacrimal dryness. From the above data it appears that patients suffering from PBC can be divided in two groups: the first comprises a small number of patients with different stages of the disease who do not show any lacrimal disorder; the second group, which is larger (78%), comprises patients with a progressive increase of lacrimal dysfunction; the positivity of the rose bengal test appears first, and it is followed by the Schirmer's test 1 and the BUT test The number of tests positive in the individual patient and the number of patients positive for all three tests progressively increases in relation to the duration of the disease.

The prevalence of lacrimal changes observed in our patients (78%) is in agreement with the data of Golding *et al.* (72%),[7] McFarlane *et al.* (69%),[8] and Alarcon-Segovia *et al.* (71%).[9] Alarcon-Segovia and colleagues reported in detail the results obtained in 14 patients with PBC. In the cases with keratoconjunctivitis sicca (71%) they found no relation either with the histological stage or with the duration of the liver disease, which was shorter than that of the present series (1–6 years compared with 1–15 years). In their study the lacrimal function was examined by the rose bengal test and the Schirmer's test 1, which was considered positive if moistening of the strip was less than 5 mm; the BUT test was not performed.

The interpretation of the results obtained by the Schirmer's test 1 is still debated because various factors can considerably affect tear formation. In a recent study performed on 100 normal subjects an average tear production of 19 mm[13] was found; men older than 55 years and women older than 60 years have a lower tear production, so that at ages between 70 and 80 years values lower than 5 mm were commonly observed in subjects without eye disorders.[14 15] Consequently one may question the interpretation of the negative findings (Schirmer's test 1 values less than 5 mm) given by Alarcon-Segovia *et al.*[9] for three patients with ages between 45 and 62 years who had been suffering from liver disease for 5–6 years. If on the contrary the limiting value of this test is fixed at 10 mm, these observations could be interpreted as confirmatory of our results.

In conclusion, most PBC patients seem to acquire the sicca syndrome. No clear-cut differences in duration or severity of liver disease are seen between patients with and without lacrimal disorders. Since the subgroup of PBC without ocular-lacrimal involvement comprises patients with a long disease duration and an advanced histological stage, it is conceivable that they will never have eye disorders. On the contrary, most patients develop lacrimal dysfunction in the early stages of the disease, starting with slight positivity of the rose bengal test and followed by progressively positive results from the other tests.

It is now known that the primary and secondary sicca syndromes (as observed in PBC) are distinct diseases, since they are associated with different immunological markers.[16] While primary sicca syndrome is linked to HLA-B8,DR3 haplotypes, no such relation has been found in secondary sicca syndrome.[17]

Whether lacrimal dysfunction in PBC is related to the same immunological mechanism responsible for biliary destruction remains to be clarified.

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British Journal of Ophthalmology, 1985, **69**, 836–840

Clinically unsuspected phacoanaphylaxis after extracapsular cataract extraction with intraocular lens implantation

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SUMMARY We describe the histopathological findings of an enucleation specimen from a clinically undiagnosed case of phacoanaphylaxis which occurred after extracapsular cataract extraction with intraocular lens implantation. Phacoanaphylaxis, a granulomatous inflammatory response to liberated lens protein, is potentially curable by prompt removal of residual lens material. This case emphasises that the diagnosis of phacoanaphylactic endophthalmitis should be considered in any case of extracapsular cataract extraction complicated by granulomatous intraocular inflammation.

In 1919 Straub[1] discussed the possibility that liberated lenticular protein could incite uveitis. In 1922 Verhoeff and Lemoine[2] introduced the term 'endophthalmitis phacoanaphylactica' for this lens-induced intraocular inflammation. Riise[3] demonstrated that phacoanaphylaxis following extracapsular cataract extraction could be dramatically arrested by prompt removal of residual lens material. We describe the histopathological findings of an enucleation specimen from a clinically undiagnosed case of phacoanaphylaxis which occurred after extracapsular cataract extraction. This case emphasises that phacoanaphylactic endophthalmitis should be suspected in any eye with persistent unexplained uveitis after extracapsular cataract extraction.

Case report

The patient was an 80-year-old female who underwent extracapsular cataract extraction in 1983 with implantation of a Simcoe anterior chamber lens. Five days postoperatively the patient had iris bombé, and laser iridotomy was performed to relieve the pupillary block. The patient continued to experience severe intraocular inflammation, suspected to be infectious endophthalmitis. This did not respond to treatment, and the eye became increasingly painful, with only light perception vision. Six weeks after cataract extraction the eye was enucleated.

PATHOLOGICAL FINDINGS

Gross examination revealed a shrunken, distorted eye which measured 24 mm in antero-posterior diameter. The sclera contained foci of haemorrhage, the cornea was cloudy, and the iris was poorly visualised. On opening the eye the vitreous was seen to be replaced by a gelatinous, dark red-brown coagulum containing a 0·5 cm roughly oval grey-white mass involving the lens remnants (Fig. 1).

On microscopic examination the cornea was noted to contain a well-healed full-thickness scar with chronic inflammatory cells, red blood cells, and extracellular pigment granules. The basal cell layer of the epithelium was noted to be oedematous. Bowman's membrane was interrupted peripherally by a fibrovascular pannus containing chronic inflammatory cells. Descemet's membrane was fragmented at the site of the cataract incision. Endothelial cells were decreased in number and a retrocorneal membrane was present. The anterior chamber was shallow and contained chronic inflammatory cells, red blood cells, and pigment granules. The iris was infiltrated by plasma cells, lymphocytes, and epithelioid cells. The iris was adherent peripherally to the retrocorneal membrane, which closed the angle on one side. Posteriorly the iris was adherent to an inflammatory mass which enveloped residual lens

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Correspondence to Daniel M Albert, MD, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, Massachusetts 02114, USA.

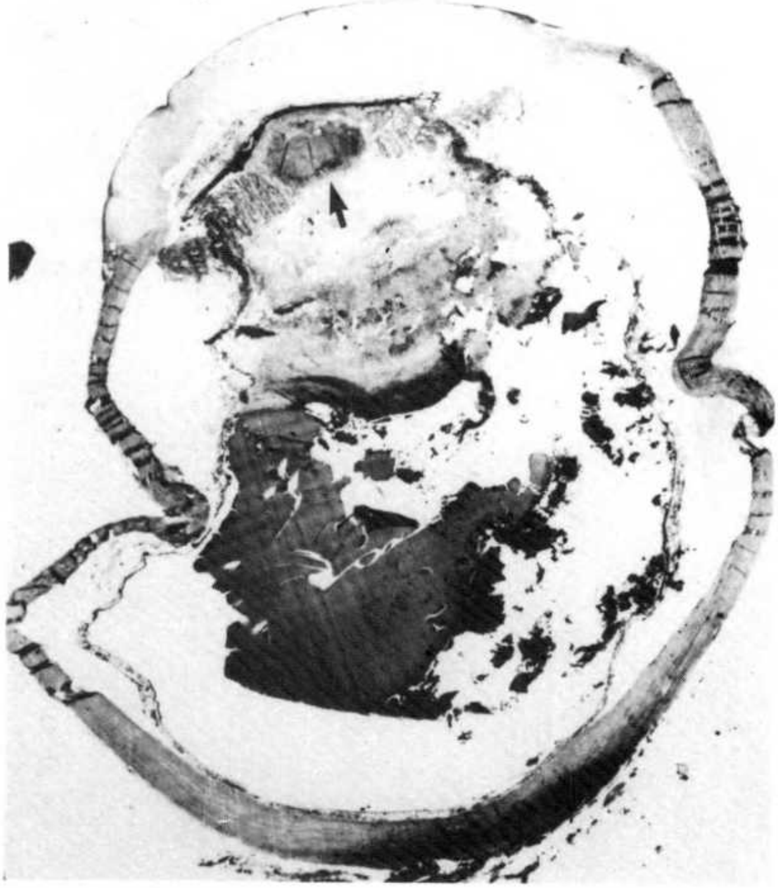

Fig. 1 *Low magnification view showing phthisical eye. Inflammatory mass (arrow) can be visualised posterior to iris. (Haematoxylin and eosin, ×7·5).*

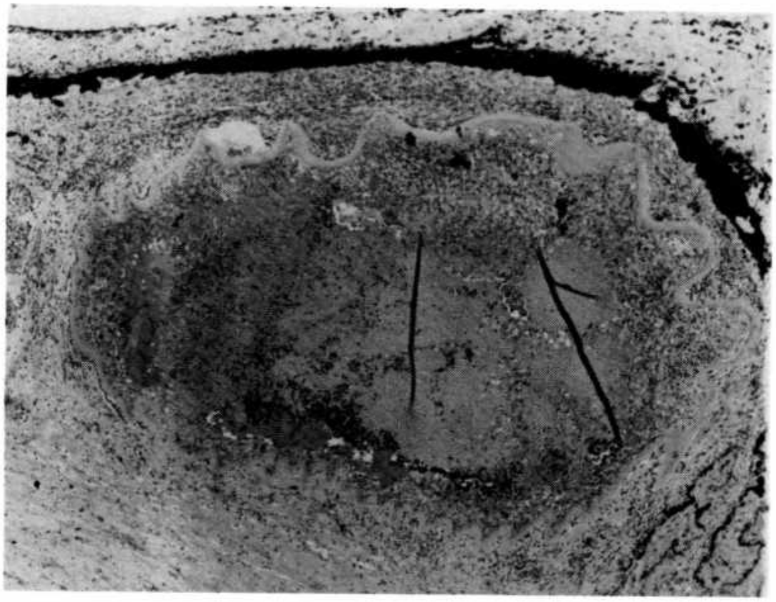

Fig. 2 *Inflammatory mass containing lens capsule and liquefied lens cortex material. (Haematoxylin and eosin, ×28).*

cortex and capsule (Figs. 2, 3). The capsule was thickened and folded. Remnants of lens cortical material demonstrated liquefaction and were infiltrated by eosinophils, polymorphonuclear leucocytes, and lymphocytes (Fig. 4). Further peripherally, epithelioid cells, giant cells, cystic spaces, and red blood cells were present (Fig. 5). The ciliary body was atrophic, hyalinised, and encased in the inflammatory mass.

The retina, which was attached in part to the inflammatory mass, was totally detached, disorganised, and atrophic. Subretinal serous fluid contained blood, non-granulomatous chronic inflammatory cells, polymorphonuclear leucocytes, pigment granules, and pigment-laden macrophages. The retinal pigment epithelium was absent in some areas. The choroid was partly detached and infiltrated by non-granulomatous chronic inflammatory cells. The sclera was folded and thickened.

Discussion

Endophthalmitis phacoanaphylactica is the term introduced by Verhoeff and Lemoine[2] for the lens-induced endophthalmitis which was previously described by Straub.[1] Phacoanaphylaxis is generally held to be an autoimmune phenomenon which occurs in response to the release of sequestered 'non-self' antigens, usually as a result of rupture of the lens capsule or possibly leakage of lens protein through the capsule. Marak and coworkers[4,5] believe that this concept does not explain why lens injury only irregularly leads to antilens antibody production nor why phacoanaphylactic endophthalmitis is such a rare disease. They contend that T cell tolerance is normally maintained by small amounts of circulating lens protein and that the pathogenesis of phacoanaphylaxis involves reversal of acquired tolerance at the T cell level. This tolerance may be altered by trauma, possibly through the adjuvant effect of wound contamination.[6]

Clinically the onset can occur as early as 1 to 14 days after leakage of lens material, and is manifest by granulomatous uveitis in the injured eye centred around the region of the lens. The inflammation may develop insidiously or acutely with congestion, a hazy cornea, white keratic precipitates, and an intense cellular exudation into the anterior chamber.[7]

The clinical diagnosis of phacoanaphylaxis, particularly in an eye with an intraocular lens implant, is difficult, and on routine examination the condition may be indistinguishable from granulomatous uveitis of other causes, or endophthalmitis. The fact that the inflammation is centred round the lens may be detected by ultrasound. Paracentesis typically reveals evidence of chronic granulomatous inflammation rather than the acute inflammation of bacterial endophthalmitis. It should be kept in mind, however, that fungal endophthalmitis can cause granulomatous inflammation. A high index of suspicion for phacoanaphylaxis in eyes with residual lens material and granulomatous inflammation is advised. Should such an eye not respond to steroid and/or antibiotic treatment, prompt removal of the residual lens would be necessary for definitive diagnosis and treatment.

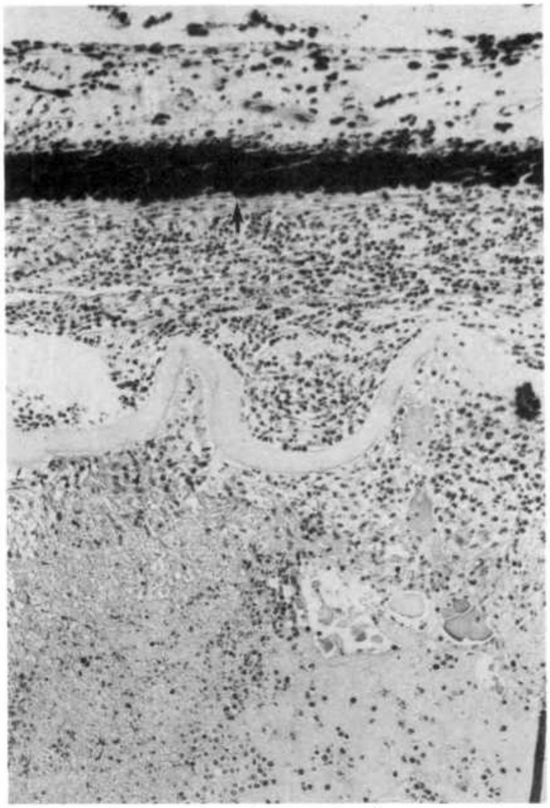

Fig. 3 *The iris (arrow) is shown to be adherent posteriorly to the inflammatory mass. The iris is infiltrated by plasma cells, lymphocytes, and epithelioid cells. (Haematoxylin and eosin, ×80).*

Histopathologically the inflammatory reaction in phacoanaphylaxis is centred round the damaged lens, which is extensively infiltrated by polymorphonuclear leucocytes and eosinophils. Surrounding the lens is a zone of epithelioid and giant cells. The adjacent iris and ciliary body are inflamed and infiltrated with lymphocytes and plasma cells.[7]

The clinician must be able to differentiate phacoanphylaxis from other complications of cataract surgery such as phacolytic glaucoma, sympathetic ophthalmia, or endophthalmitis. In phacolytic

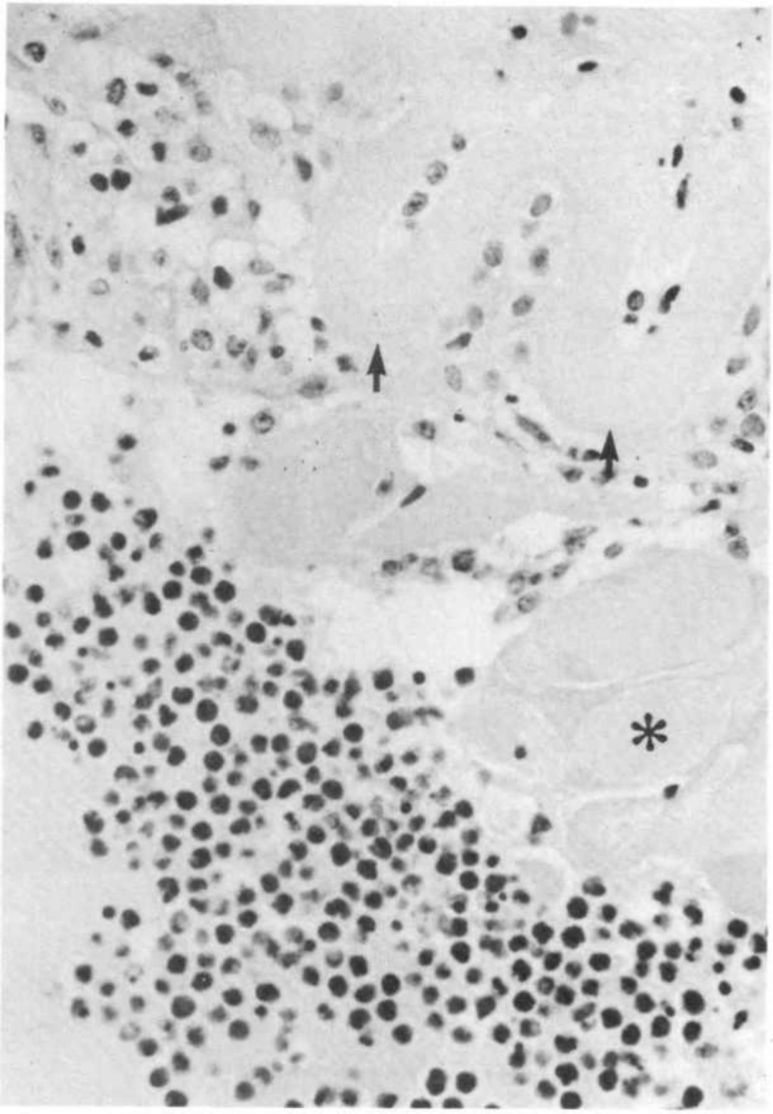

Fig. 4 *High magnification of acute inflammatory reaction around folded lens capsule (arrows) and liquefied lens cortex material (asterisk). (Haematoxylin and eosin, ×200).*

glaucoma, macrophages engorged with lens material become lodged in the trabecular meshwork. The clinical picture consists of a severe increase of intraocular pressure with cells in the anterior chamber. Keratic precipitates and posterior synechiae, often seen with phacoanaphylaxis, are typically absent. Sympathetic ophthalmia is a bilateral, granulomatous panuveitis which usually occurs two weeks[8] or more after accidental or iatrogenic injury. The injured eye appears irritated and injected shortly after surgery, culminating in a picture of persistent bilateral uveitis characterised by 'mutton fat' keratic precipitates, iris and pupillary nodules, posterior synechiae, and the appearance of yellow-white Dalen-Fuchs nodules in the periphery of the fundus. Approximately one-fourth of phakic eyes enucleated for sympathetic ophthalmia show evidence of phacoanaphylaxis.[9] The signs and symptoms of bacterial endophthalmitis are generally present 18–72 hours after surgery and include increasing pain, hyperaemia, chemosis, lid and corneal oedema, anterior chamber and vitreous inflammation, and a decreased or absent retinal reflex.

If phacoanaphylaxis is left untreated, an unremitting downhill course of chronic inflammation may ensue, ultimately leading to synechiae, cyclitic mem-

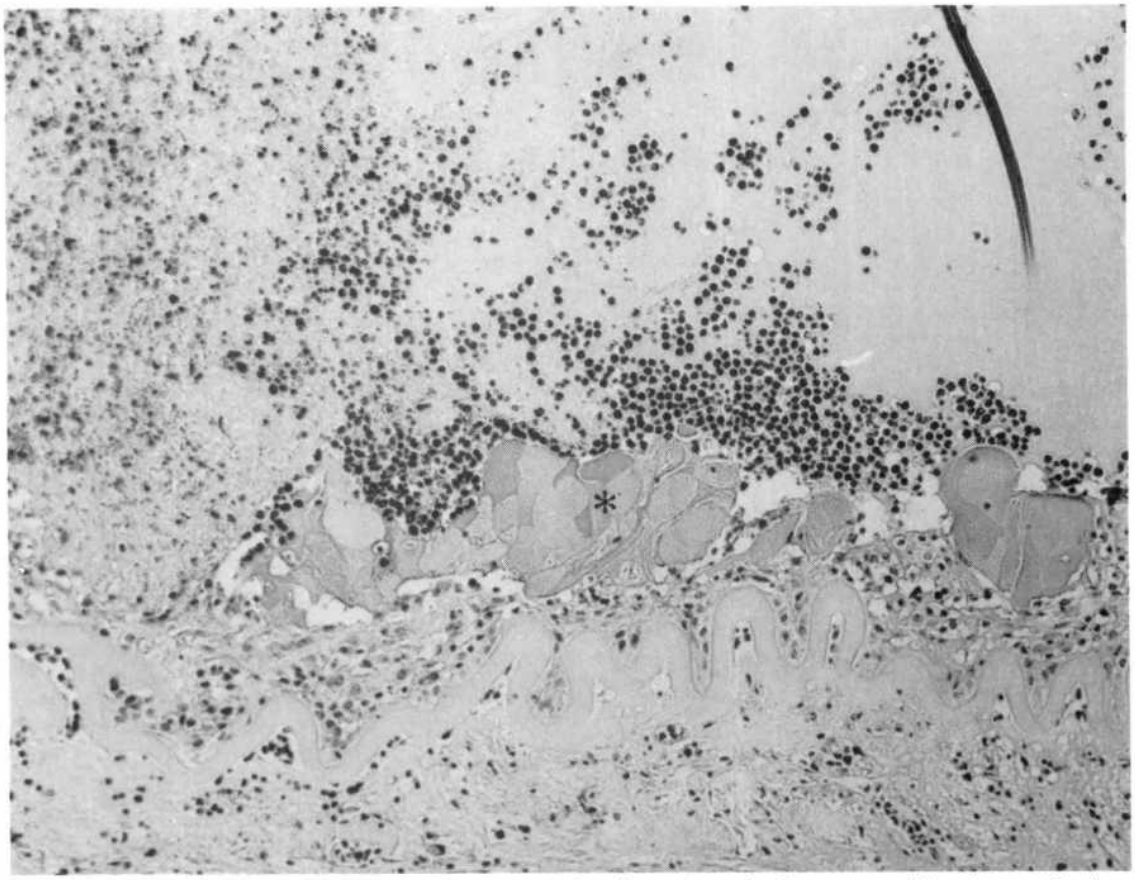

Fig. 5 *Liquefied lens cortex (asterisk) infiltrated by eosinophils, polymorphonuclear leucocytes, and lymphocytes. Further peripherally, chronic granulomatous inflammatory cells are present. (Haematoxylin and eosin, ×100).*

brane, retinal detachment, and phthisis bulbi. In any case of extracapsular cataract extraction complicated by a granulomatous intraocular inflammation the diagnosis of phacoanaphylaxis should be seriously considered. The ability to differentiate phacoanaphylaxis from phacolytic glaucoma,[10] sympathetic ophthalmia,[11] or endophthalmitis has important therapeutic implications.

The present report is to the best of our knowledge the first case occurring after an intraocular lens implant. Since the majority of these procedures are at present performed with extracapsular extractions, lens cortex may be left in the eye. The occurrence of phacoanaphylaxis is therefore not surprising and must be considered in this type of surgery.

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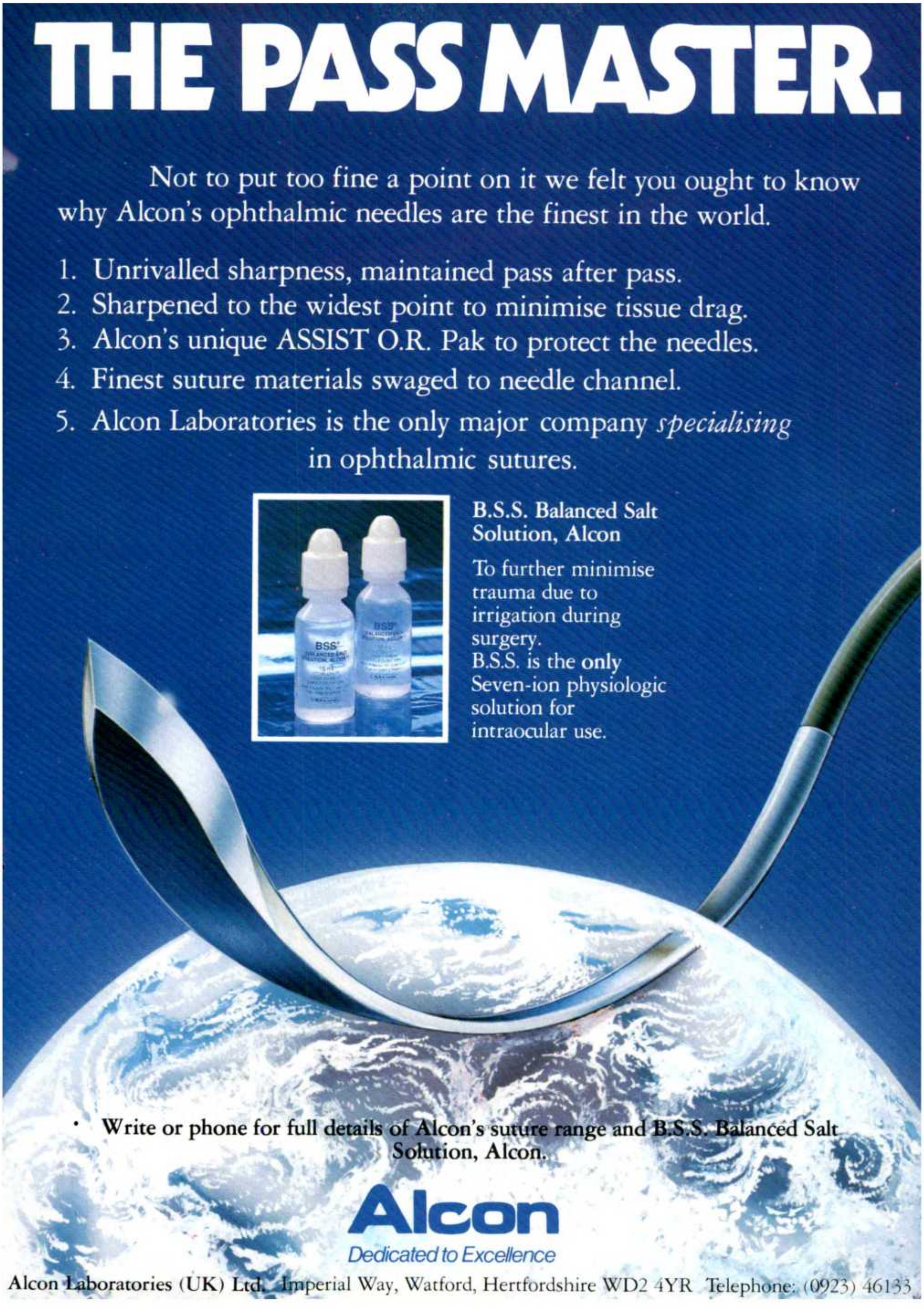

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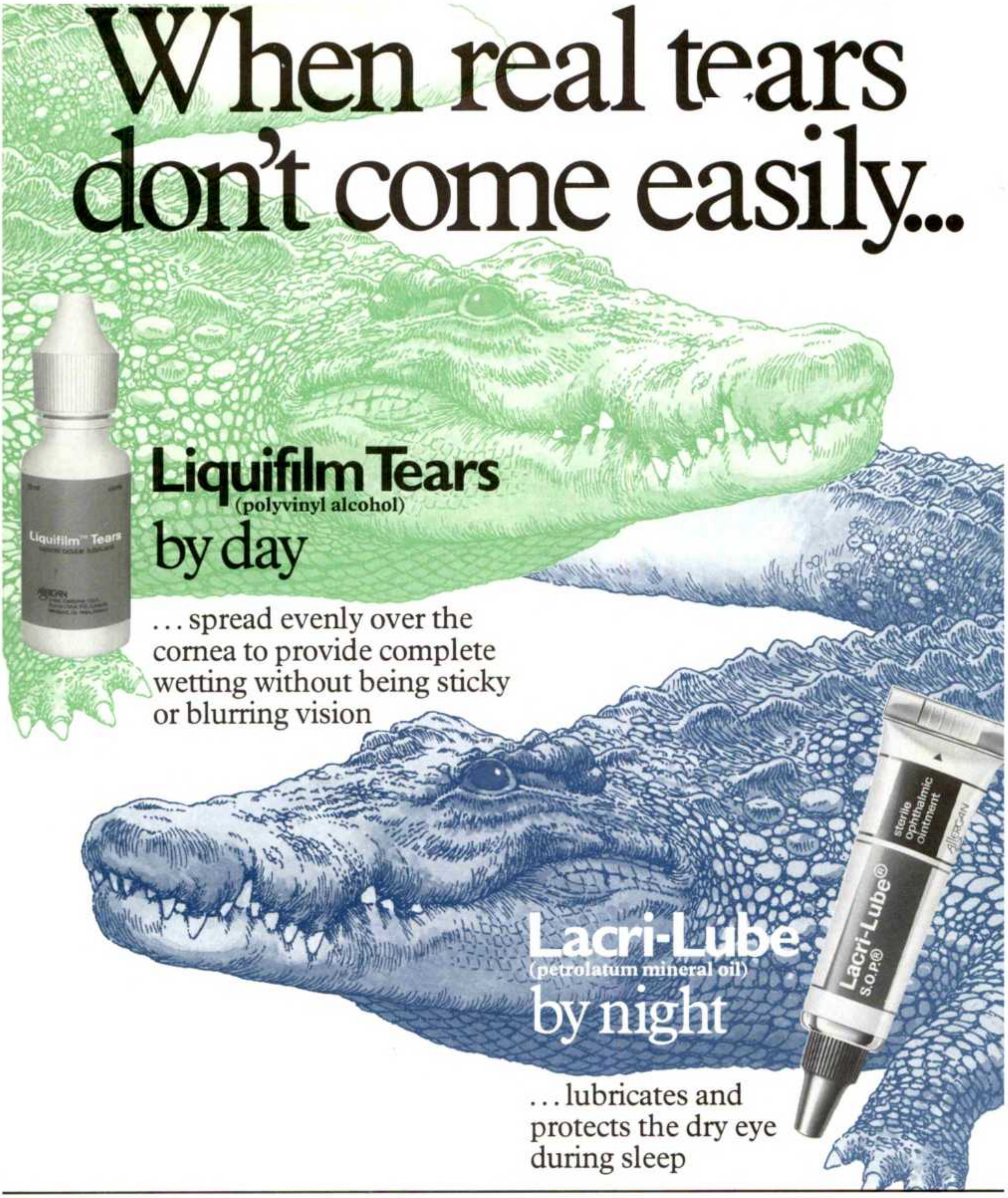
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Role of the posterior capsule in the prevention of postoperative bacterial endophthalmitis: experimental primate studies and clinical implications*

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SUMMARY The posterior capsule has an important effect on the risk of postoperative bacterial endophthalmitis. In order to investigate whether the posterior capsule inhibited the spread of infection into the vitreous we performed extracapsular cataract extraction in both eyes of 10 primates. In one eye of each primate the posterior capsule was left intact and in the other eye a large posterior capsulectomy was performed. When the anterior chambers were challenged with equivalent inocula of *Staphylococcus aureus*, one of 10 eyes with an intact posterior capsule developed culture-positive vitreous infection. In contrast, nine of 10 eyes with a large posterior capsulectomy developed culture-positive vitreous infection. In a second experiment we investigated the effect of an intraocular lens on the barrier effect. Ten primates received extracapsular cataract extraction in both eyes and pseudophakic implantation. In one eye of each primate the posterior capsule was left intact and a J-loop monoplanar lens was implanted in the ciliary sulcus. In the other eye of each primate a large posterior capsulectomy was followed by implantation of a monoplanar, non-vaulted pseudophakos into the anterior chamber. None of the 10 eyes with a posterior capsule intact and a posterior chamber lens in place developed positive vitreous cultures or histopathological evidence of vitreous infection. Thus the presence of a posterior chamber lens did not appreciably compromise the barrier effect of the intact posterior capsule. 40% of eyes with a large posterior capsulectomy and a non-vaulted pseudophakos in the anterior chamber developed culture-positive vitreous infection, and 60% of the eyes showed histopathological evidence of vitreous infection.

Unfortunately, scant attention has been paid in recent years to the prevention of postoperative bacterial endophthalmitis Retrospective clinical studies suggested that preoperative topical antibiotics reduce the incidence of postoperative bacterial endophthalmitis.[1,2] There is no scientific proof, however, that modern topical antibiotic regimens actually reduce the incidence of postoperative bacterial endophthalmitis. Some surgeons, therefore, do not use preoperative antibiotics.[3]

Other than these retrospective, uncontrolled studies which seemed to show that certain preoperative topical antibiotics can be effective in reducing the incidence of postoperative bacterial endophthalmitis there have been no quantitative studies demonstrating the clinical efficacy of other preventive measures. In part this is because such clinical trials would require a vast number of cases.

There has been a legitimate concern that the growing popularity of extracapsular cataract surgery could result in a rise in the number of cases of postoperative bacterial endophthalmitis. Multiple entries into the eye and the infusate are added sources of intraoperative contamination There are reasons to suspect that extracapsular surgery which preserves the posterior capsule intact may be safer than if the posterior capsule is violated. Maylath and Leopold previously showed that in the phakic eye

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*Presented in part at the American Academy of Ophthalmology Meeting, Chicago, Illinois, November 1983

Correspondence to Francis E O'Donnell Jr, Md, 3663 Wendell Blvd, St Louis, Missouri 631 08, USA inoculation of bacteria into the anterior chamber was much less effective in producing bacterial endophthalmitis than was vitreous inoculation.[4] During an era when intracapsular cataract extraction was used in the vast majority of cases, Forster[5] and others reported cases of postoperative bacterial endophthalmitis in which the anterior chamber culture was negative but the vitreous culture was positive, suggesting that the anterior chamber is somehow better able to control infection than is the vitreous cavity. From these observations we reasoned that the posterior capsule might act as a physical barrier to the spread of organisms into the vitreous cavity, and that if the organisms could be confined to the anterior chamber they might be more effectively overcome by the body's defense mechanisms. If this were the case, we considered that the clinical implications would be far-reaching.

Material and methods

EXPERIMENT 1

In the first experiment we performed extracapsular cataract extraction in both eyes of 10 adult primates (rhesus and cynomologus). The details of the surgical technique are published elsewhere.[6] The anterior capsulotomy was large, extending to the edge of the fully dilated pupil. The cortical clean-up was meticulous. In one eye of each primate the posterior capsule was left intact. In the other eye a large posterior capsulectomy (estimated to be at least $9\ mm^2$) with no or only minimal anterior vitrectomy was performed with a vitrector inserted through the limbus. Minimal vitrectomy was performed if the anterior hyaloid was disrupted. To exclude intraoperative contamination we waited two weeks postoperatively before challenging the anterior chamber of each eye with an equivalent inoculum of *Staphylococcus aureus*.

Two weeks after surgery all eyes were found to be quiet, with clear media. Conjunctival chemosis and/or hyperaemia was absent. No eye had any clinical sign of endophthalmitis. The technique for preparation of the inocula has been reported in detail elsewhere.[6] Appropriate dilutions were made accordingly to obtain 10^3 or 10^4 organisms per 0·05 ml of saline. Microbial concentrations were verified at the time of preparation by inoculating known volumes of suspension on blood agar plates and performing counts after 24 hours.

After intramuscular injection of ketamine HCL a 'bevel-up injection' (that is, with the port of the needle facing towards the cornea and not towards the vitreous cavity) was carefully made into the anterior chamber of each monkey eye through the surgical wound, and 0·05 ml was injected. After inoculation each animal was examined by handlight by two observers who had no previous knowledge of which eye had undergone capsulectomy. Their clinical examinations were recorded every 24 hours for 72 hours. At 72 hours after inoculation all animals were killed and the anterior chamber and central vitreous cavities were cultured separately by aseptic techniques. The anterior chamber was cultured by using a translimbal approach to aspirate 0·1 ml, and the central vitreous cavity was cultured by a pars plana approach to aspirate 0·5 ml. The specimens were immediately inoculated on to blood agar plates. Cultures were judged to be positive if even a single colony of phage-typed *Straphylococcus aureus* was isolated on the streak. The globes were then hemisected and the vitreous cavities were examined with the dissecting biomicroscope (Fig. 1). The

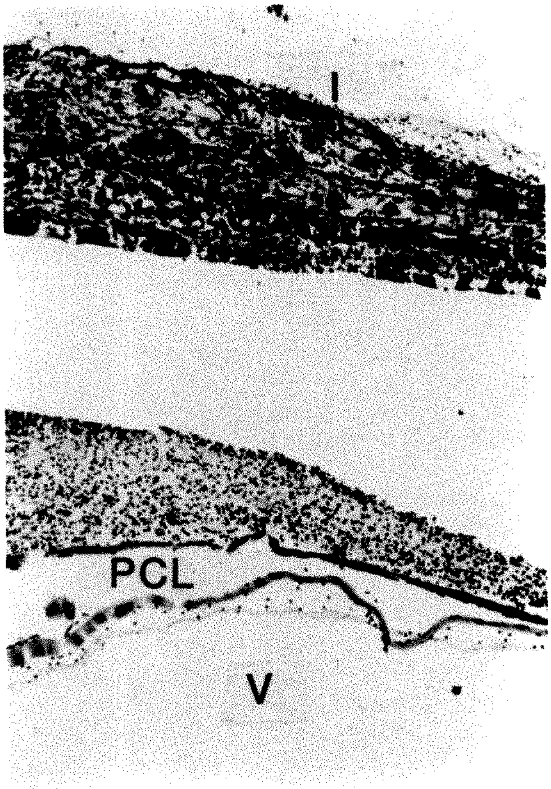

Fig. 1 *Primate eye which had received extracapsular cataract extraction with intact posterior capsule and posterior chamber implant. The iris (I) is intensely infiltrated with inflammatory cells. The inflammatory exudate was layered on the anterior surface of the implant (PCL), which was dissolved in the paraffin embedding. The intact posterior capsule is present with a few inflammatory cells in the anterior vitreous (V). PCL=posterior chamber implant cavity, I=iris, V=vitreous. (Haematoxylin and eosin).*

primate organs were then used by other investigators at the St Louis University School of Medicine.

EXPERIMENT 2

In the second experiment we wanted to determine if the presence of a posterior chamber lens in any way affected the protective barrier effect of the intact posterior capsule. Moreover we investigated whether or not a non-vaulted monoplanar lens would provide some protective barrier effect to the spread of infection from the anterior chamber into the vitreous cavity. Extracapsular cataract extraction was performed in both eyes of 10 primates. In one eye of each of 10 primates the posterior capsule was left intact, and a J-loop monoplanar lens was inserted into the posterior chamber. It was our clinical impression that the lens was inserted into the ciliary sulcus and not into the capsular bag. In the other eye extracapsular cataract extraction was then followed by posterior capsulectomy (estimated to be at least 9 mm^2) with minimal anterior vitrectomy by means of a vitrector through the limbus, and then a monoplanar lens (non-angulated J-loop lens) was inserted into the anterior chamber. No peripheral iridectomy was performed. Two weeks after the operation the anterior chambers were challenged with equivalent inocula of *Staphylococcus aureus* organisms, as in study 1. 10^4 organisms in 0·05 ml, as in study 1, were injected into the anterior chamber of each eye. Clinical observations by handlight were made at 24-hour intervals for 72 hours. At 72 hours the animals were killed, the anterior chambers were cultured with a translimbal aspiration of aqueous and with a pars plana aspiration of the central vitreous cavity, as in study 1. The globes were then submitted for gross pathological and histopathological study

Results

EXPERIMENT I (Table 1)

Monkey 1 had an inoculation of each eye with 10^3 *Staphylococcus aureus* organisms and failed to develop infection in either eye. Therefore in the remaining primates we chose to use a dose of 10^4 *Staph. aureus* organisms. None of the nine eyes which had an intact posterior capsule developed biomicroscopic evidence of vitreous inflammation. Nevertheless, one eye with an intact capsule had a positive vitreous culture for *Staph. aureus* (a single colony on the blood agar plate). All nine eyes with extensive posterior capsulectomy developed biomicroscopic evidence of vitreous inflammation, and all nine eyes had positive vitreous cultures for *Staph. aureus*. By Fisher's exact test the disparity between the two groups could have occurred by chance with a probability of less than 0·00021.

Table 1 *Results of experiment 1*

	Capsule intact	*Capsulectomy*
No of eyes	10 eyes	10 eyes
Anterior chamber culture positive	5	5
Vitreous culture positive*	1	9
Vitreous inflammation	0	9
Anterior chamber culture positive and vitreous culture negative	4	0

*$p<0·00021$

EXPERIMENT 2 (Table 2)

None of the 10 eyes with the posterior capsule intact and with the posterior chamber lens in place developed positive vitreous cultures. Moreover gross pathological and histopathological study of these specimens did not show evidence of vitreous infection. There was no significant spread of lens epithelium on to the posterior capsule. By contrast, in four of the 10 eyes with capsulectomy and pseudophakos in the anterior chamber there were positive vitreous cultures. Moreover in six of the eyes there was biomicroscopic and histopathological evidence of inflammation within the vitreous cavity (Fig. 2). Analysis of culture results by Fisher's exact test showed that the difference between the two groups was statistically significant at $p<0·043$.

Discussion

We chose to challenge the experimental eyes with *Staphylococcus aureus* for two reasons. Firstly, *Staph. aureus* is an important cause of virulent postoperative bacterial endophthalmitis.[7] Secondly, it is more virulent than some other bacteria responsible for postoperative bacterial endophthalmitis, such as *Staph. epidermidis*. We reasoned that if a protective barrier effect could be demonstrated for *Staph. aureus*, it was likely that this same barrier effect would exist for less virulent organisms. Certainly the visual prognosis for eyes with postoperative bacterial endophthalmitis due to *Staph. aureus* is much worse than for *Staph. epidermiditis*.[7]

Table 2 *Results of experiment 2*

	Capsule intact and posterior chamber lens	*Capsulectomy and anterior chamber lens*
No of eyes	10 eyes	10 eyes
Anterior chamber culture positive	4 eyes	7 eyes
Vitreous culture positive*	0	4
Vitreous inflammation	0	6
Anterior chamber culture positive and vitreous culture negative	4	3

*$p<0·043$

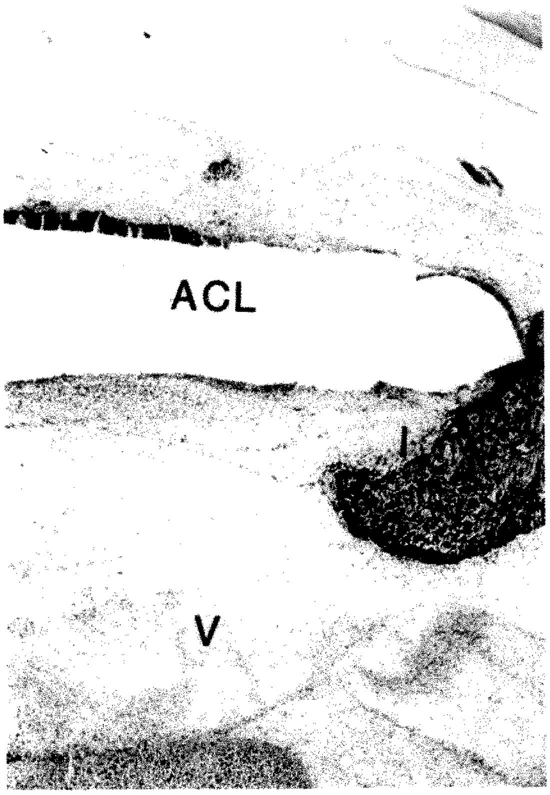

Fig. 2 *Primate eye which had received extracapsular cataract extraction with posterior capsulectomy and anterior chamber implant (ACL). A massive inflammatory exudate surrounds the implant cavity with intense vitritis (V). ACL=anterior chamber implant cavity, I=iris, V=vitreous. (Haematoxylin and eosin).*

The first primate experiment showed that the intact posterior capsule does have a protective barrier effect. It inhibits the spread of bacterial infection into the vitreous cavity. By helping to confine the infective organisms in the anterior chamber it allows the body's natural defence mechanisms to control the infection more adequately. Certainly the posterior capsule is a relative and not an absolute barrier to the spread of infection from the anterior chamber to the vitreous cavity. In the second animal experiment we showed that this protective barrier effect of the intact posterior capsule was not appreciably compromised by the presence of a posterior chamber lens which had been implanted into the ciliary sulcus. The clinical implications of these experimental primate studies are numerous.

Firstly, primary or secondary surgical posterior capsulotomies should be avoided if at all possible. In Hurite's series, for example, several patients developed bacterial endophthalmitis following secondary surgical posterior capsulotomy.[8] Delayed non-invasive opening of the posterior capsule with a YAG laser is preferred, because it disrupts the barrier without a concomitant inoculation of bacteria. Other than superior ease of performance, this is at present the most compelling reason for using the YAG laser for posterior capsulectomy rather than surgical posterior capsulotomy, since the rates of other complications may not differ significantly, though Keates *et al.* have recently reported that the incidence of cystoid macular oedema may be less with YAG posterior capsulectomy.[9] Since suture removal for irritation or to control astigmatism may be associated with bacterial endophthalmitis,[7] YAG posterior capsulectomy should be delayed until further suture removal is unlikely.

Secondly, cataract cases at particular risk for endophthalmitis, such as cases of penetrating corneal laceration and traumatic cataract, should have the posterior capsule preserved if at all possible. Translimbal vitrectors are often used to treat such cases, but unless the surgeon encounters formed vitreous he should studiously avoid indiscriminate removal of the posterior capsule.

Thirdly, in cases with filtering blebs, the risk for delayed postoperative endophthalmitis is significant (albeit related to the type of filtration bleb[10 11]), and the posterior capsule should be left intact if at all possible. Therefore in patients with filtration blebs who have developed significant cataracts we strongly recommend the use of extracapsular surgery, especially if the bleb is cystic and thin-walled.[3] For these same reasons in patients undergoing combined cataract and filtration surgery we also recommend extracapsular surgery.

Fourthly, what if the posterior capsule eventually opacifies? Although this study did not investigate whether the size of the capsulotomy would have an influence on the protective barrier effect of the posterior capsule, it seems likely to us that small, centrally placed YAG capsulectomies are more desirable than large capsulectomies. If a posterior chamber lens is present, this may act to 'seal' the small, centrally placed posterior capsulectomy, as suggested by Simcoe (personal communication) and by our own studies.[12] In a previous study we found that only one of five primate eys which had received extracapsular cataract extraction, posterior chamber implant, and a posterior capsulotomy developed endophthalmitis after the injection of 10^3 *Staph. aureus* into the anterior chamber. In this eye the posterior capsulotomy extended inadvertently beyond the edge of the optic, whereas in the other four eyes the posterior capsulotomy had been smaller and did not extend beyond the edges of the optic.

Therefore, if a secondary capsulotomy is necessary, we recommend the use of a small, centrally placed capsulectomy with the YAG laser. If a posterior chamber lens is present, the capsulectomy should not extend beyond the edges of the optic. In glaucomatous eyes with active filtration this also reduces the risk of vitreous prolapse into the filtration site.

Fifthly, the barrier effect of the intact posterior capsule means that we must begin to modify our approach to the postoperative patient who develops intraocular inflammation. It is important to note (see Tables 1 and 2) that some anterior chamber cultures were positive (7 out of 20 eyes) in the primate eyes with intact posterior capsule although the vitreous was culture negative. Once again this underscores the barrier effect of the intact capsule. It also suggests that we may begin to appreciate clinically a type of postoperative endophthalmitis which is confined to the anterior segment ('anterior endophthalmitis') and which does not require direct vitreous therapy.[7] The combination of frequent topical antibiotics and intravenous antibiotics may suffice, especially when the organism is *Staphylococcus epidermidis*.[13] In clinical practice we now examine such patients at the slit-lamp in order to study their anterior vitreous. In a series of over 500 extracapsular cataract extraction with posterior chamber implant and intact posterior capsule cases we have not personally seen a cellular response in the anterior vitreous prior to three weeks postoperatively, when some sterile anterior vitritis is occasionally visible on biomicroscopy. Therefore a cellular reaction in the vitreous of eyes with an intact posterior capsule within the first week postoperatively would be interpreted as a grave sign of possible infection, with spread of infected material into the vitreous, and our management would be more aggressive, including vitreous tap or vitrectomy and intravitreal antibiotics. Although it has been suggested that in the aphakic patient the vitreous cavity can be cultured through a translimbal approach following aspiration of aqueous, our studies strongly suggest that it would be unwise to culture the vitreous cavity through the limbus by penetrating the posterior capsule with a needle and aspirating vitreous. Such a manoeuvre would probably enhance the spread of any infected material into the vitreous cavity. In eyes with extracapsular cataract extraction and intact posterior capsule the vitreous cavity should be cultured by a pars plana approach.

Sixthly, when the posterior capsule is inadvertently disrupted, the risk of infection is greater. Unfortunately, when an extracapsular cataract extraction is complicated by vitreous loss, this usually occurs prior to removal of all cortex. In some series 'unplanned extracapsular cataract extraction' (that is, cataract extraction that has vitreous admixed with retained cortex) has a threefold higher risk of bacterial endophthalmitis than does an uncomplicated intracapsular cataract extraction.[1] We recommend immediate pars plana vitrectomy for complicated extracapsular cases with retained cortical material admixed with formed vitreous, and with significant intraocular inflammation, for three reasons: (1) there is an increased risk of bacterial endophthalmitis in this situation; (2) it can be virtually impossible early on to determine clinically whether or not this is sterile inflammation or infection; (3) the inflammation induced by the retained cortex in the vitreous reduces the visual potential. In Jaffe and Clayman's series,[14] for example, the chances of cystoid macular oedema are significantly greater with vitreous loss in extracapsular cataract extraction than with vitreous loss in intracapsular cataract extraction. Pars plana vitrectomy reduces the inflammatory load of retained cortex. Although a pars plana vitrectomy has usually been reserved for management of bacterial endophthalmitis which is unresponsive to intravenous and intracameral antibiotics for the reasons just cited, we personally feel that a pars plana vitrectomy should be used promptly in complicated extracapsular cases with suspected endophthalmitis

Seventhly, any intraocular manipulation in the anterior segment after cataract surgery carries the risk of bacterial endophthalmitis, so an intact posterior capsule is desirable. For example, in patients who elect not to have intraocular lens implantation at the time of cataract surgery, but who may later decide to have intraocular lens implantation because of difficulties with contact lenses or aphakic spectacles, extracapsular surgery with an intact posterior capsule would seem to reduce the chances of bacterial endophthalmitis during secondary implantation. This would be true regardless of whether the implant chosen was angle-supported or in the posterior chamber. A YAG posterior capsulectomy should be deferred if possible, until after it is clear that the patient can tolerate contact lenses or aphakic spectacles.

In conclusion, these experimental studies demonstrate yet another important effect of the intact posterior capsule. In addition to lowering the incidence of cystoid macular oedema[14] and reducing the chances of rhegmatogenous retinal detachment, at least in axial myopes,[15] the intact posterior capsule provides some protection against bacterial endophthalmitis after extracapsular surgery.

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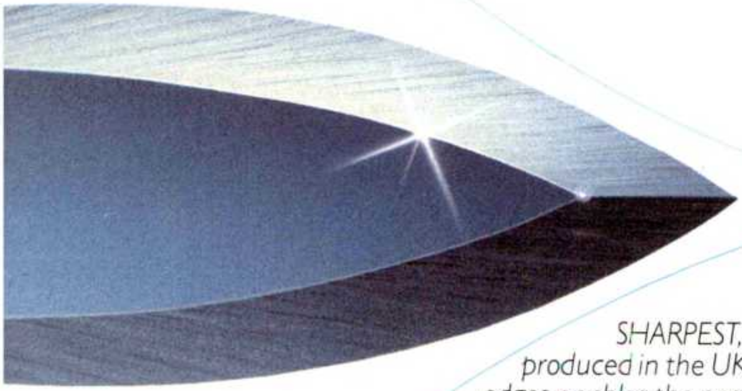

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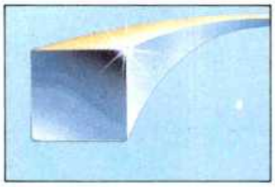

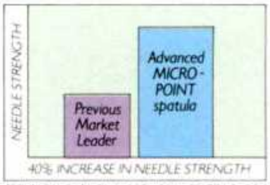

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British Journal of Ophthalmology, 1985, **69**, 847–850

Randomised double-blind trial of acyclovir (Zovirax) and adenine arabinoside in herpes simplex amoeboid corneal ulceration

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A PATTERSON,[2] AND P J REES[3]

From the Royal Victoria Eye and Ear Hospital, Dublin; St Paul's Hospital, Liverpool; and the Wellcome Research Laboratories, Kent.

SUMMARY Fifty-one patients were treated in a dual-centre, double-blind comparison of acyclovir and adenine arabinoside in herpetic amoeboid (geographic) corneal ulceration. Twenty-four of the 25 patients receiving acyclovir healed in a mean time of 12·2 days, while 24 of the 26 patients treated with adenine arabinoside healed in a mean time of 11·0 days. There was no statistically significant difference between the two groups in terms of healing. A second analysis, excluding any patients who had received antiviral treatment immediately prior to entry into the study, showed that 18 of the 19 who received acyclovir healed in an average of 11·7 days and 18 of the 19 recipients of adenine arabinoside healed in a mean time of 11·2 days. Again the difference was not statistically significant.

Acyclovir (Zovirax) is a highly selective and relatively non-toxic antiherpes agent.[1,2] It has become a standard treatment for dendritic corneal ulceration over the past few years and is at least as effective as[3-5] or superior to[6-10] idoxuridine (IDU) and adenine arabinoside (Ara-A) and broadly similar to trifluorothymidine (TFT)[11]. Acyclovir also has a role in the management of stromal herpetic keratitis.[12]

Geographic (amoeboid) corneal ulceration is a much more difficult problem than dendritic ulceration. It is frequently associated with the previous use of corticosteroids and is often complicated by deep keratitis and anterior uveitis. Topical administration of acyclovir ophthalmic ointment has been shown to produce potentially therapeutic levels of the drug in the aqueous humour,[13] which may be of benefit in the treatment of geographic ulceration. In this paper the role of acyclovir in the management of herpetic geographic corneal ulceration is examined and its efficacy is compared with that of Ara-A.

Materials and methods

Two centres were involved in this study. Patients presenting with geographic ulcers and who gave their informed consent were included. Each patient was randomly allocated to receive either 3% acyclovir, or 3% Ara-A in ointment form, together with cycloplegics and eye padding as appropriate. The ointments were applied five times daily until the healing of the lesions and then for a further three days. Both drugs were identically packaged and coded. Patients were seen as frequently as necessary but at least twice weekly. At each visit a full ocular examination was carried out. The ulcer was stained and its size measured, the extent and severity of any stromal reaction and uveitis were recorded, and symptoms were scored on a points basis (0–3). Healing was reached when there was no further staining of the ulcer area. Patients were withdrawn from the study if the ulcer worsened over three days or remained static for more than 10 days. Patients were to be withdrawn if any toxic signs or symptoms appeared.

The treatment groups were compared on entry for distribution of sex, ulcer size, occurrence of previous attacks, and previous therapy by χ^2 tests. Age and symptom duration, and severity of symptoms, stromal infiltration, and uveitis were compared by Mann-Whitney tests. A number of patients had received antiviral treatment before entry into the study, and, as it was felt that this might prejudice the results, a separate analysis was performed by the same methods but with the exclusion of these patients.

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Table 1 *Characteristics of patients at presentation*

		All patients		*Patients with no previous antiviral therapy for this attack*	
		Adenine arabinoside	*Acyclovir*	*Adenine arabinoside*	*Acyclovir*
Sex	Male	13	16	7	11
	Female	13	9	12	8
Ulcer size	Small	18	7	14	5
	Large	8	18	5	14
Previous attack	Percent	52	40	42	42
Age (years)	Median	57	54	61	45
Duration of symptoms (days)	Median	14	10	11	7
Severity of symptoms (score)	Mean	2·0	2·0	2·0	1·9
Stromal infiltration (score)	Mean	1·2	1·1	1·3	1·0
Uveitis (score)	Mean	0·5	0·8	0·7	0·9
Previous therapy this attack	Corticosteroid	6	3	6	3
	Antiviral	7	6	0	0
	Antibiotic	4	8	3	8

Results

Fifty-four patients entered the study. Three patients randomly allocated to acyclovir treatment failed to return after their initial assessment and were excluded from the analysis. Of the 51 remaining patients 26 received Ara-A and 25 acyclovir. Characteristics of the patients at entry are summarised in Table 1. Statistical analyses showed no significant differences between the two groups at entry, except that the acyclovir group had a significantly higher proportion of patients with large ulcers than the Ara-A group ($p<0·05$). A number of patients were receiving corticosteroids or antibiotics on entering the study.

Three patients were withdrawn from the study owing to failure of treatment, two in the Ara-A group and one in the acyclovir group. The lesions in all the remaining patients healed. Log rank analysis of the two treatment groups showed no significant difference in healing times. The mean healing time for the Ara-A group was 11·0 days, and for the acyclovir group, 12·2 days ($p=0·62$; Fig. 1). Owing to the imbalance in ulcer size between the two groups at entry, an analysis with treatment and ulcer size as factors was carried out. This showed no effect of ulcer size on healing time. Previous steroid therapy for the current attack did not appear to influence healing times. The only adverse reaction noted was superficial punctate epitheliopathy in two patients receiving acyclovir and five patients receiving Ara-A.

Seven patients treated with Ara-A and six on acyclovir had received antiviral treatment immediately prior to entry into the study. It was possible that

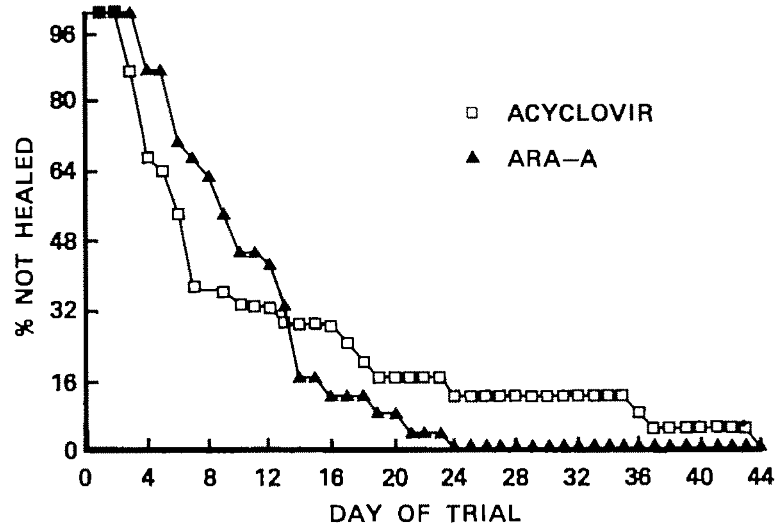

Fig. 1 *Cumulative frequency distribution of time taken to heal.*

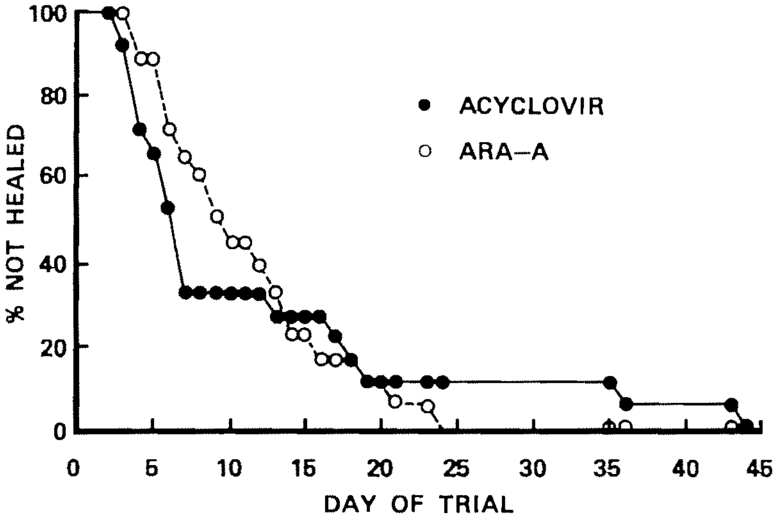

Fig 2 *Cumulative frequency distribution of time taken to heal (apart from patients with previous antiviral therapy for the current attack).*

this might prejudice the results, so a separate analysis was performed with these patients excluded. The characteristics of the remaining patients are summarised in Table 1. The acyclovir group again had a significantly higher proportion of large ulcers than the Ara-A group ($p<0{\cdot}01$), but there were no other significant differences between the two groups at entry. The mean healing time in the Ara-A group was 11·2 days as compared with 11·7 days in the acyclovir group ($p=0{\cdot}39$; Fig. 2).

Discussion

Geographic corneal ulcers are difficult to treat and are associated with many complications. They frequently require more prolonged therapy than simple dendritic ulcers. Many are associated with previous corticosteroid therapy, which complicates their management. It is important therefore that these lesions are managed with an agent which can be used for as long as necessary and with no toxic effects. It is clear that prolonged treatment with IDU is associated with significant toxicity. Acyclovir should be a suitable agent because of its solubility and low incidence of toxicity.

This study has shown that acyclovir and Ara-A are effective and of equal potency in the management of geographical herpetic corneal ulceration. Healing rates were not affected by either ulcer size or the previous use of antiviral agents. The previous use of corticosteroids did not appear to influence the healing'times. No significant toxic effects were recorded in either group.

Previous experience with acyclovir has not been associated with any significant side effects even when given for up to 61 days.[9] Acyclovir therefore is particularly suitable for the treatment of amoeboid corneal ulceration, which frequently requires more prolonged treatment than simple dendritic ulceration.

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A first attempt to prevent amblyopia and squint by spectacle correction of abnormal refractions from age 1 year

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SUMMARY Spectacle correction of unusually hypermetropic refractions from age 1 year did not reduce the incidence of squint or amblyopia, nor did it lead to a reduction in the severity of residual amblyopia after subsequent occlusion.

The ability to predict which children are particularly likely to present subsequently with esotropia and/or amblyopia[1] is an essential precursor to exploring the possibility of preventing these conditions. However, there is no point in prediction if prevention is impossible. Many children who present with squint and/or amblyopia have hypermetropic refractions at the time they present,[2] and the first step in treatment is optical correction of these refractions. Since the only method of predicting squint/amblyopia was identification of hypermetropia at age 1 year,[1] it seemed logical to try optical correction of abnormal refractions from that age in the hope that squint/amblyopia might be prevented. This had been suggested before,[3-5] but so far as we are aware this is the first attempt to do it.

Patients and methods

The children reported on here were drawn from two population samples: (1) Children born in an around the town of Kettering. Those born in 1974–7 were refracted after cycloplegia with 1% atropine twice daily for four days, and their refractions have already been reported.[6] Those born in 1978 were refracted after cycloplegia with cyclopentolate 1%. (2) Children born in the town of Rushden in the years 1975–8 who were refracted after cycloplegia with cyclopentolate 1%. The refractions of those born in 1975 and 1976 have also been reported.[7]

PROTOCOL FOR THE TRIAL

The refractive criteria for entry into the trial were either or both of (*a*) bilateral spherical hypermetropia of +2·00 DS or more; (*b*) anisometropia of +1·00 or more D sphere or cyl.

Once a child had been identified as having an abnormal refraction, the mother was told that her child had a refraction which we thought was unusually likely to lead to the appearance of squint and/or amblyopia. It was not known whether spectacle correction would prevent these conditions, but, if she wished, her child could enter a trial designed to show if this was possible. It was explained that the rules of the trial required that her child would be randomly allocated to wearing glasses or not, but that she had to decide whether she wished to enter the trial before the random decision for 'treatment' or 'no treatment' was taken. The child, treated or not treated, would then be followed up every three months until the age of 3½ years or soon thereafter, when it would be possible to obtain an accurate assessment of vision. If in the meantime squint was detected, conventional treatment would be given.

If a child entered the trial and was randomly allocated to wear glasses, the prescription of the glasses was based on the cycloplegic retinoscopy with 2·00 D subtracted from each meridian of each eye. Spectacles were prescribed until refraction came within normal limits, that is, <+2·00 DS right and left, <+1·50 D cyl, <1·00 DS or cyl anisometropia.

This protocol lacked many of the features of an ideal controlled trial, principally because the future course of events was unknown. For example, it was

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impossible to plan the number of children to be included in the trial, because it was not known what proportion of children allocated spectacles would wear them, and it was impossible to speculate on what the drop-out rate would be.

One hundred and forty-nine children did not enter the trial. Those living in Kettering were not followed-up, but those in Rushden were reviewed at age 3½. Further information is available on 44 of these children. The incidence of visual defects does not differ from those included in the trial.

CONDUCT OF THE TRIAL

Every attempt was made to encourage regular review, but many attendances followed reminders sent through the post and it was impossible to achieve the ideal. Some of the children who were lost to follow-up moved from the area, but some information has been obtained from colleagues elsewhere in the UK. Others dropped out but reattended after a final recall about the age of 3½ years or returned spontaneously because of squint or poor performance at a school vision screening test. A final vision was recorded for 265 of the 306 children who originally entered the trial.

Recording of compliance with treatment presented difficulties. Although one could be reasonably sure when children were obviously wearing glasses or not, sometimes one could do no more than guess how much or whether treatment was being given.

The end result was to be decided on the basis of: (*a*) Presence or absence of esotropia/intermittent esotropia; (*b*) presence or absence of amblyopia at the age of 3½. This has not proved possible in practice.

ASSESSMENT AND RECORDING OF RESULTS

Our experience since this trial started in January 1975 made it necessary to change the original plan for presenting the end results. The reasons for this were as follows. (1) Uncertainty about the visual acuity of young children, particularly around the age of 3½.[8] (2) Uncertainty about making a definite diagnosis of amblyopia, particularly if a child had been given occlusion before visual acuity was known and acuity subsequently became normal. (3) Uncertainty about compliance with treatment. This could be ignored if it is accepted that the correct purpose of the trial should have been to assess the effect of *prescribing* spectacle treatment. The results of the 'treatment' group have been subdivided into two groups, namely, T+ and T±/0 where there were doubts about whether treatment was being given or not. (4) The amount of meridional hypermetropia[1] had been identified as a better predictive indicator than bilateral spherical hypermetropia and/or anisometropia (meridional hypermetropia is the amount of hypermetropia in the most hypermetropic meridian).

Therefore the end result has been recorded as the last known visual acuity of the eye with lower acuity, with spectacle correction if necessary, and after occlusion had been given and often some time after occlusion had stopped.

The two groups of children (those screened after atropine and those screened after cyclopentolate) have been pooled after allowance was made for the (approximate) 0·5 D[7] difference between a refraction after atropine and after cyclopentolate. The refraction recorded represents the cyclopentolate equivalent of the highest amount of meridional hypermetropia at age 1 year.

Table 1 *Children with <+3·50 D at age 1 year*

		6/6	*6/9*	*6/12*	*6/18*	*6/24*	*6/36*	*6/60 or less*	*Unknown*
T+	No Squint	44(1)	12	1	1	—	1	—	2
	Squint	4(1)	—	—	—	—	—	—	—
T±/T0	No Squint	21	8	—	1	—	—	—	16
	Squint	1(1)	—	—	—	—	—	—	—
NT	No Squint	51	31(1)	—	—	—	—	—	13
	Squint	6(1)	4(3)	1(1)	1(1)	—	1(1)	—	—

Figures in parentheses show numbers of children who had occlusion

Table 2 *Children with +3·50 or more D at age 1 year*

		6/6	*6/9*	*6/12*	*6/18*	*6/24*	*6/36*	*6/60 or less*	*Unknown*
T+	No Squint	3	6(1)	3(2)	1(1)	—	—	1(1)	—
	Squint	5(1)	—	1(1)	2(2)	2(1)	—	1(1)	—
T±/T0	No Squint	3(2)	3	1(1)	—	—	—	—	5
	Squint	—	1(1)	1	—	—	1	—	—
NT	No Squint	9(1)	12(1)	1	2(1)	2(2)	—	—	5
	Squint	2	3(1)	4(1)	1(1)	1(1)	2(2)	2(2)	—

Figures in parentheses show numbers of children who had occlusion

Table 3 *Incidence of squint*

	T+	*T±/0*	*NT*
No squint	73	37	108
Squint	15	4	28

Results

Tables 1 and 2 summarise the findings, indicating the refraction at age 1 year (more or less than +3·50 D meridional hypermetropia) and the last known visual acuity, the presence of squint, and whether occlusion had been given. Table 3 records the incidence of squint.

The incidence of squint among all those drawn for Treatment irrespective of whether treatment was given or not was 19 out of 129. This is less than the incidence of squint in those drawn for 'no treatment', 28 out of 136, but the difference is not significant ($p=0{\cdot}28$).

Discussion

The findings in this series of children confirm three observations made previously[1,9]: (1) amblyopia is more predictable than squint; (2) amblyopia is significantly related to meridional hypermetropia at age 1 with a cut off point at +4·00 D (atropine) or +3·50 D (cyclopentolate).

Unfortunately, however, it is clear that spectacle correction of hypermetropia or hypermetropic anisometropia from age 1 year has not contributed to the prevention of squint and/or amblyopia. Even after additional occlusion treatment the acuity of the 'treated' group was the same as in the 'untreated' group. It must be said, however, that only one-quarter of those who had occlusion had it before age 3½ years. This was because in many cases visual acuity was not assessed before 3½. It will never be known whether the final acuity of these children would have been improved by earlier and perhaps more enthusiastic occlusion therapy.

Our previous paper[9] drew attention to the observation that children who are likely to end up (under current methods of management) with the most severe amblyopia are potentially identifiable because of highly abnormal refractions in 3·7% of the population at age 1 year.[9] Better results might be achieved if we knew why this particular project failed. Four possible explanations come to mind. Firstly, occlusion was given too late and not enough was given. We think it would not be easy, in practice, to demonstrate that earlier occlusion would be more effective, particularly in those children who do not have additional indicators of severe amblyopia such as constant uniocular squint or considerable hypermetropic anisometropia. It is worth pointing out that amblyopia does not inevitably follow uncorrected hypermetropic anisometropia at age 1 year. Secondly, the known facts about form vision deprivation during a sensitive period may not be relevant to the aetiology of squint and amblyopia in the absence of ocular disease such as congenital cataract. However, if they are relevant, the sensitive period may be effectively over by 1 year, and preventive treatment at this age may have been given too late. Thirdly, it is possible that our traditional basic management (spectacle correction of abnormal refractions, particularly hypermetropia) of squint/amblyopia is wrong. Fourthly, in some instances squint and amblyopia may be due to congenital/familial neuronal abnormalities somewhere along the visual pathway and that these happen to be associated with congenitally determined refractive abnormalities.

The easiest one of these to explore is the possibility of earlier optical correction of hypermetropia, and this is currently being tried from the age of 6 months.

We wish to thank the general practitioners and their health visitors for enabling us to study the children under their care We also thank Mrs L A Neale and Mrs D Maddams for their secretarial help

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Effect of hyperthermia on experimental choroidal melanoma

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SUMMARY Thirty-five rabbit eyes were implanted subchoroidally with Greene's hamster melanoma. When the tumours reached a base diameter of 5 mm, they were treated with ultrasonically induced hyperthermia with a range of temperatures and exposure durations (43–67°C and 75 s to 60 min). Of the 23 treated eyes examined two months after treatment eight showed complete regression of the tumour. Seven showed initial tumour regression, but there was subsequent regrowth of tumour round the margins of the original mass. In eight eyes the tumour continued to grow, though in some cases the rate of growth appeared to be slower than in the controls. In contrast, in all untreated animals the tumour grew to fill the vitreous cavity. These preliminary findings indicate that ultrasonically induced hyperthermia can be an effective local treatment of this intraocular tumour model.

The tumoricidal effect of hyperthermia either alone or in conjunction with radiotherapy is well known.[1] Heat treatment of tumours has ranged from the use of hot waterbaths[2] to regional perfusion with warmed blood.[3] Modern methods of inducing selective heating of tissues has involved radiofrequency electromagnetic waves,[4] microwaves,[5,6] and ultrasound techniques.[7,8] This paper describes local, ultrasonically induced hyperthermia (UIH) in the treatment of experimental choroidal melanoma. We describe the model and define temperature and exposure duration relationships required to kill Greene's hamster melanoma growing in the choroid of rabbits.

Material and methods

Thirty-five eyes of 26 rabbits (New Zealand White and Dutchbelt strains weighing between 2 and 3 kg) were studied.

An experimental model of choroidal melanoma was prepared by a modification of Krohn and colleagues' technique.[9] The tumour stock used was a strain of amelanotic Greene's melanoma[10] maintained by serial transplantation into the anterior chamber of rabbit eyes. The tumour was dissected from the iris stroma of the freshly enucleated eye and placed in F10 tissue culture medium. It was minced into pieces measuring approximately 1 mm^3. Thirty minutes prior to implantation the tumour fragments were removed from the medium and dried on cellulose spears, which reduced the volume and increased the consistency of the implanted tissue. The recipient rabbits were then anaesthetised (intramuscular ketamine 100 mg and xylazine 10 mg). The eye was rotated inferotemporally with a limbal traction suture. A conjunctival peritomy was made in the superonasal quadrant, and a small scleral flap was dissected approximately 6 mm posterior to the limbus, forming a pocket. The incision was deepened to expose the choroid. Tumour fragments were inserted into the subchoroidal space with a 20 gauge lumbar puncture needle with a polished tip and recessed trocar. The scleral flap was closed over the tumour with a running suture and the operative field irrigated with water to remove or lyse any free tumour cells on the episclera. Tumour growth in the choroid was monitored by indirect ophthalmoscopy.

Ten rabbits underwent phacoemulsification prior to tumour implantation. This improved visualisation of the tumour through the cornea while the eye was immersed in the waterbath during treatment. Refrac-

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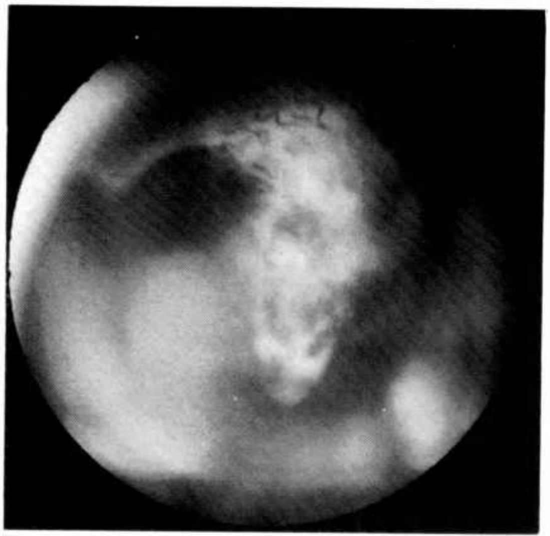

Fig. 1 *Fundus photograph showing elevated mass of Greene's melanoma in rabbit choroid prior to treatment.*

tive and absorptive effects of the lens on the ultrasound beam were avoided, and the growth of the tumour into the vitreous was unimpeded by the large lens of the rabbit.

The tumours took an average of two weeks to attain a base diameter of approximately 5 mm and a height of 3 mm. At this stage the tumour was judged to be suitable for treatment. As the tumour grew, it was usually surrounded by a localised exudative retinal detachment or retinal neovascularisation (Fig. 1).

A therapeutic ultrasound system designed specifically for ophthalmic use[11] was employed. The therapeutic transducers were spherically curved shells. Two transducers were used, one of diameter 42 mm and the other of 80 mm. Each had a 90 mm focal length and was operated at its third harmonic (4·6 MHz). Included in this assembly was a coaxial 7·5 MHz diagnostic ultrasound transducer used to obtain biometric data and a fibreoptic light source for visual orientation of the centre of the ultrasound beam. A coupling bath arrangement was used to provide low loss transmission between the eye and ultrasound transducer by means of a plastic drape slipped over the proptosed eye of the anaesthetised rabbit.[12] The therapeutic transducer was manually positioned, and the desired distance from transducer to the surface of the tumour was read from the diagnostic A scan.

The temperature was monitored throughout the procedure by means of copper-constantan thermocouples mounted in 29 gauge needles. The thermocouples were connected to a digital thermometer module (Bailey Instruments BAT-8). Three thermocouples were used during each treatment. The reference thermocouple was inserted under direct visualisation through the sclera into the tumour centre. A second thermocouple was inserted into the sclera overlying the tumour base in the aphakic rabbits. In the phakic rabbits it was inserted into the sclera opposite the tumour in the region of the exit of the ultrasound beam from the eye. A third thermocouple was placed in the coupling bath. The tumour temperature was kept constant throughout the procedure by monitoring the output of the reference thermocouple and making appropriate adjustments in the excitation voltage applied to the ultrasound therapeutic transducer. Temperature readings from all three thermocouples were taken every minute during treatment. The tumour temperature showed only minor fluctuations during therapy; the average variation from the desired temperature was ±0·9°C. The average temperature gradient from tumour to sclera in the aphakic rabbits was 4·3°C with a range of 1–13°C. In the phakic rabbits the average temperature gradient across the eye was 6·2°C, with a range of 3–9°C.

The coupling bath medium consisted of normal saline initially heated to 37°C and allowed to cool during the procedure. The 80 mm transducer was positioned so that its focal point was situated 12 mm in front of the anterior tumour surface in the aphakic rabbits (10 eyes). This midvitreous focusing provided a relatively uniform intensity across the width of the tumour; the effective (half power) beam width at the site of the tumour was 10 mm (Fig. 2A). In the phakic rabbits (17 eyes) the 42 mm transducer was used with a lateral orientation, and the focal point was positioned approximately 12 mm external to the sclera (Fig. 2B). This arrangement reduced the dose of ultrasonic energy to the lens.

Treatment regimens used tumour temperatures ranging from 43 to 67°C and exposure durations of 75 seconds to 60 minutes. These values were based on the tissue destruction results of in-vivo experiments with local hyperthermia in the treatment of other mammalian tissues.[13]

Eight eyes were implanted with tumour to serve as controls and shams. The four controls were kept for observation following implantation. The other four eyes served as shams—that is, they were given sham hyperthermia treatments. Under anaesthesia the implanted eye was proptosed, surrounded by the saline bath, and the thermocouples were inserted. This configuration was maintained for one hour, but no ultrasound treatment was delivered.

Controls, shams, and treated animals were maintained for observation for as long as three months after tumour inplantation. The effects of treatment

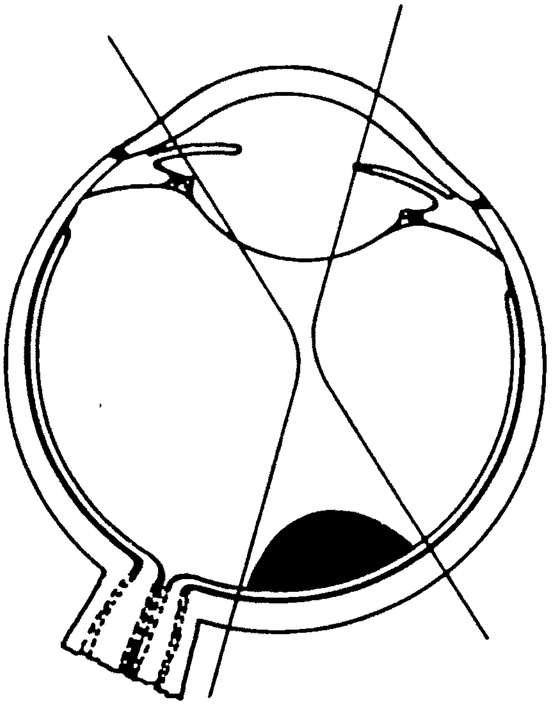

Fig 2a *Arrangement of ultrasound beam in relation to tumour in an aphakic rabbit.*

were assessed daily during the first week, twice weekly for a month, and then weekly until the animal was killed.

Results

In all animals in the control and sham groups, the tumour grew to fill the vitreous space without regression.

In the treated eyes minimal changes were observed immediately following therapy, most often slight blanching of the tumour with occasional subretinal haemorrhage. During the first week after treatment most eyes developed localised subretinal haemorrhage on the surface of the tumour, and the pre-existing exudative retinal detachment increased. Small vitreous haemorrhages, which usually did not prevent further fundus observation, were seen in a few animals.

During the second week after treatment it became possible to distinguish three main responses to hyperthermia. In the responsive group (eight eyes) the tumour shrank with resolution of the exudative detachment and haemorrhage. The site of the tumour eventually appeared as a flat area of chorioretinal atrophy. In the initially responsive group (seven eyes) there was an early response with regression of the tumour to a flat scar, but recurrence at the margin of the original tumour mass was seen up to six weeks after treatment. In the non-responsive group (eight eyes), the tumour mass continued to grow. In some of these eyes the rate of growth of tumours appeared slower than the rate of growth of tumours in the control and sham groups. The temperature and exposure duration relationships are plotted in Fig. 3 for a series of 23 eyes: the tumour regression patterns observed are noted by different symbols.

Histopathological examination with light microscopy confirmed the funduscopic observations. In successfully treated cases a flat chorioretinal adhesion developed. The retina was atrophic in the region of the tumour and appeared normal in the adjacent areas (Fig. 4). Implantation of the tumour resulted in sclera thinning at the tumour site. The ultrasound intensities used in this study were much lower than in our previous work, where focused ultrasound was used to produce chorioretinal and

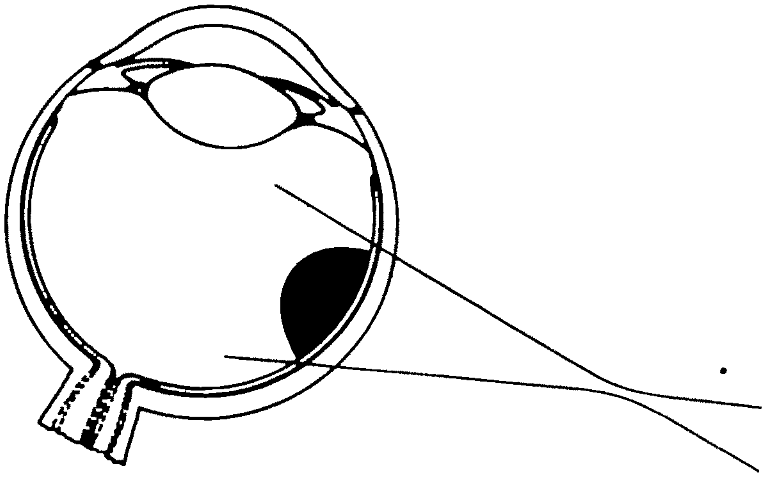

Fig. 2b *Arrangement of ultrasound beam in relation to tumour in a phakic rabbit.*

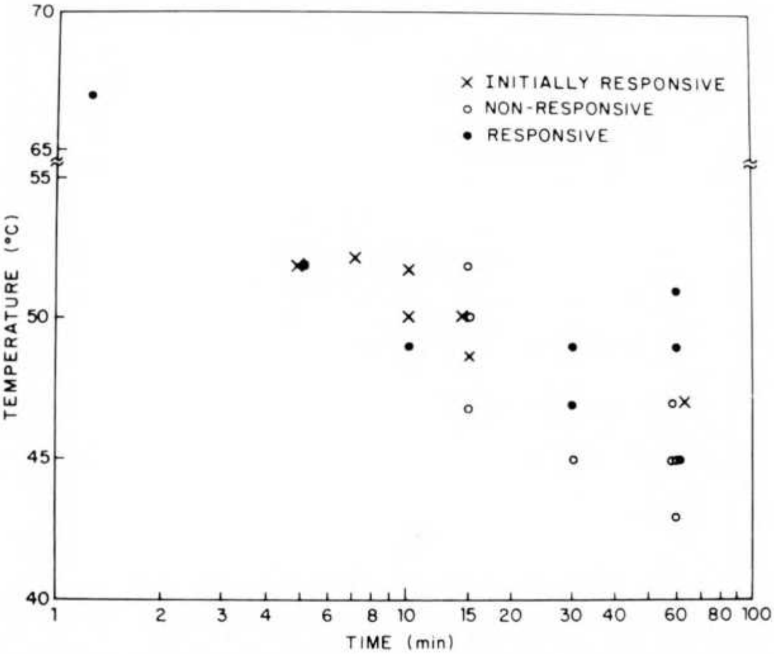

Fig. 3 *Graph demonstrating the relationship between temperature and exposure duration. The regression patterns observed are noted by different symbols.*

scleral lesions.[14] Gliosis of the optic nerve was observed in some eyes where the tumour was in close proximity to the nerve head. In non-responsive eyes the tumours contained large areas of malignant cells mixed with areas of necrosis and haemorrhage. There were numerous mitoses. Scleral infiltration with extrascleral extension was occasionally seen at the site of tumour implantation in sham, control, and

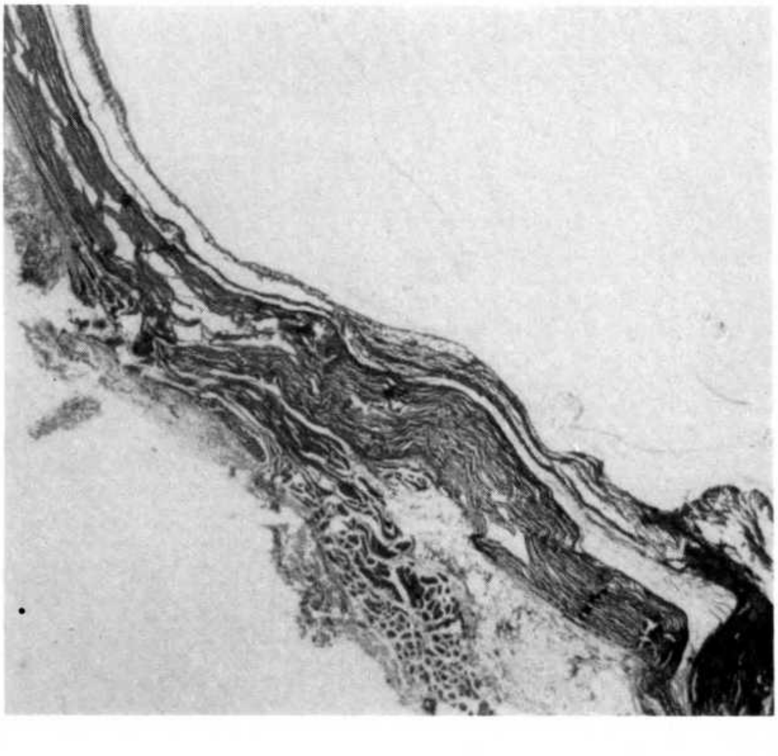

Fig. 4 *A flat choroidal retinal adhesion with normal surrounding retina after successful treatment with ultrasound-induced hyperthermia. (H and E, ×20).*

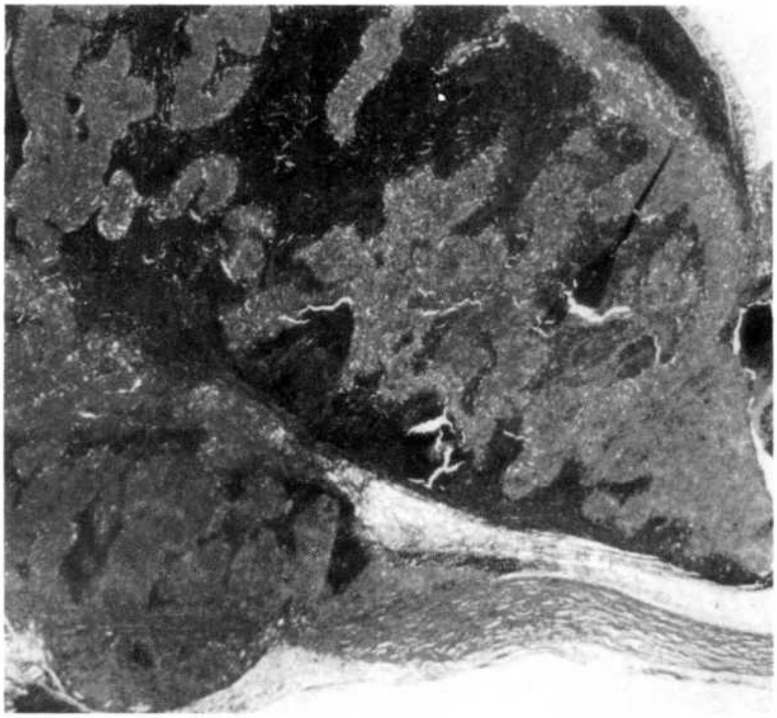

Fig. 5 *Areas of malignant cells with necrosis and haemorrhage in a non-responsive eye. (H and E, ×20).*

non-responsive eyes (Fig. 5). This was probably due to the presence of the implantation tract. There was no histological evidence of damage to the cornea, iris, or lens in any of the 23 eyes treated with either the 42 or 82 mm transducer which did not develop immediate post-treatment problems (vide infra).

Four eyes developed complications from the treatment resulting in inability to evaluate the effect of treatment and are not included in Fig. 3. The most serious complication was orbital oedema with secondary proptosis and lagophthalmos, noted 24 hours after treatment. Corneal exposure with resultant ulceration and/or opacification was the outcome in each of these cases. In seven phakic animals with high-temperature short-duration treatment (>49°C, 5–15 min) scleral thinning was observed. In one case scleral melting was seen in the region where the ultrasound beam exited from the eye. Two types of retinal detachment were seen after UIH. In the majority of animals a localised exudative detachment either developed or increased during the first week after treatment. This resolved in the cases where the tumour regressed but increased in eyes containing non-responsive tumours. Seven of the treated phakic eyes developed a rhegmatogenous retinal detachment. As discussed in the next section, these complications were associated with a set of experimental conditions peculiar to the rabbit model.

Discussion

These findings indicate that UIH alone can be an effective local treatment of this intraocular tumour model. It must, however, be noted that this rapidly growing strain of hamster melanoma with its propensity for sarcomatous change is pathologically different from the slow growing human choroidal melanoma. Initial tumour regression was observed at temperatures of 45°C for one hour. Complete regression was most frequently observed at treatment temperatures of 49°C for one hour. Other workers have reported that temperatures of 42°C to 47°C maintained for one hour have resulted in irreversible damage in rodent and rabbit tumours.[13] Several factors may account for the higher temperatures required to obtain total tumour regression in this work. Most recurrences were observed at the border of the tumour. It is possible that the choroid adjacent to the margin of the tumour could allow greater heat dissipation and establish a temperature gradient between the core of the tumour and its periphery. Thus a subtherapeutic temperature would be present at the tumour borders. Secondly, in our study the eye was proptosed and surrounded by a saline bath initially heated to 37°C but allowed to cool during the procedure. The thin sclera of the rabbit may also allow excessive heat dissipation into the adjacent waterbath medium. Marginal recurrence of tumour may also be related to inaccurate beam orientation resulting in an edge of the tumour being inadequately heated.

The complications of UIH seen in this study were primarily related to beam orientation. The occasional severe orbital swelling and secondary proptosis were probably a consequence of the anatomical location of the proptosed globe, with subsequent difficulty in the accurate and perpendicular positioning of the ultrasound beam in some animals. Specifically, the proptosed rabbit eye rests against the bony orbital rim, which can result in very high local temperatures for several reasons. Firstly, the orbital bone will reflect virtually all the incident ultrasound, doubling the local intensities and temperature elevations. Secondly, bone, unlike soft tissue, can support ultrasonic shear waves, and the incident compressional ultrasonic wave can be converted to shear waves at the bone surfaces. These shear waves are strongly absorbed by adjacent soft tissues causing very high local temperatures. In the human, acoustic attenuation within the orbital fat will greatly reduce the intensity levels at the orbital wall, and such phenomena should be negligible. Subretinal haemorrhage and exudative retinal detachment, which were observed after treatment in most animals, may have been the result of vascular damage produced by the relatively high temperatures used in this study. The rhegmatogenous retinal detachments seen in seven phakic eyes most likely resulted from inadvertent perforation of the retina by the thermocouple.

It is believed that hyperthermia has multiple actions at a cellular level and on tumour microcirculation. Histologically, tumours treated with hyperthermia show hypertrophy of the Golgi apparatus and an increase in acid-phosphatase-positive lyzosomes six hours after treatment.[15] Later this destruction becomes more widespread, as evidenced by derangement of the cytoplasm and rupture of plasma membranes. In addition there is denaturation of enzymes necessary for DNA repair as well as direct inhibition of DNA, RNA, and protein syntheses.[16]

The tumour microvasculature also has an important role in the heat sensitivity of malignant cells. Charateristically the centre of the tumour mass has a sluggish blood flow, whereas in the periphery it may be rapid owing to low tissue pressure and short capillary lengths. Song *et al.* demonstrated that in normal tissues (skin and muscle of rats) the blood flow increased three- to four-fold when heated to 43°C for one hour.[17] At higher temperatures vascular breakdown occurred. However, tumours heated to these temperatures showed no increase in blood flow but more often a decrease in perfusion. At 45°C stasis of blood flow within tumours is observed, with infarction and coagulative necrosis.[18] Reduction of blood flow may reduce the supply of nutrients to the tumour and slow the egress of cellular breakdown products after hyperthermia. As a secondary effect there is an increase in aerobic glycolysis and lactic acid production. The resulting decrease in intracellular pH within the tumour may result in activation of lyzosomal enzymes which damage membranes of organelles within the cell.

While this work has evaluated hyperthermia as a sole form of treatment, in current medical practice heat treatment is usually given in combination with radiation therapy. The rationale behind this is the well known synergistic effect between radiation and hyperthermia in the treatment of malignant disease.[19] This synergism is of potential benefit in ophthalmology, where the most common intraocular tumour, choroidal melanoma, is relatively radioresistant. Focal hyperthermia supplied by ultrasound energy might thus be particularly useful when combined with localised radiation—for example, cobalt plaque to achieve tumour regression with reduced radiation dosage. Initial studies in our laboratory with ophthalmologically relevant human tumour xenographs in athymic nude mice confirms this synergistic effect.[20]

The authors acknowledge the assistance of Dr W Harrison and Dr F Jakobiec with the interpretation of histopathological material and thank Miss Elizabeth Maher for her help in the early stages of this study

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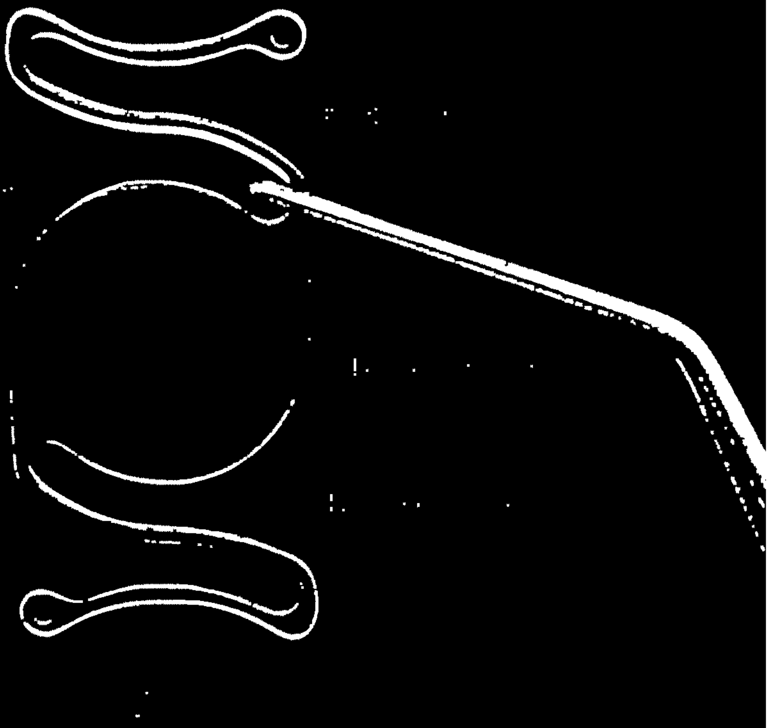

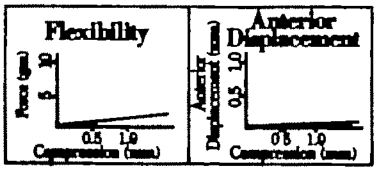

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Unilateral eyelid, conjunctival, and choroidal tumours as initial presentation of diffuse large-cell lymphoma

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SUMMARY Simultaneous ipsilateral eyelid, conjunctival, and choroidal tumours developed in an otherwise healthy man. Biopsy of the eyelid mass led to the diagnosis of large-cell lymphoma. Further examination revealed systemic lymphoma. Although the ocular and adnexal lesions responded to systemic chemotherapy, additional skin tumours later developed. Large-cell lymphoma (also called reticulum cell sarcoma and histiocytic lymphoma) is becoming increasingly recognised for its ophthalmic manifestations. The clinical signs, diagnostic investigations, and treatment of this disease are discussed.

Large-cell lymphoma (also known as reticulum cell sarcoma and histiocytic lymphoma) has recently gained considerable attention in the ophthalmic literature. It is the lymphoma with the greatest frequency of ocular involvement. There are basically two forms of this malignancy. The first type, with frequent intraocular involvement, is likely to present as a persistent uveitis.[1] It is usually associated with central nervous system (CNS) tumour and no systemic disease. However, the more common type of large-cell lymphoma is the diffuse systemic form. Although ocular adnexal and orbital involvement is often reported, intraocular manifestations are considerably less frequent.

It is well documented that patients with systemic lymphoma may present initially with eyelid involvement.[2,3] However, we were unable to find any reports of both intraocular and adnexal tumour together preceding systemic signs. This paper describes a patient who we believe is the first to present initially with simultaneous eyelid, conjunctival, and choroidal large-cell lymphoma before systemic disease was obvious.

Case report

In September 1983, an 80-year-old previously healthy white man was referred to the Oncology Service of Wills Eye Hospital. His past ocular history was negative except for uncomplicated intracapsular cataract extractions in 1959 and 1975 in the left and right eyes respectively, and ocular-sparing left facial herpes zoster in 1971. His family history was unremarkable.

Eight weeks prior to our consultation he had noted slight tearing from his left eye. The patient's ophthalmologist noted a mass in the left brow and several ipsilateral fundus lesions. Metastatic carcinoma was suspected, and a laboratory and radiological survey was ordered. However, chest x-ray, complete blood count, blood chemistry tests,

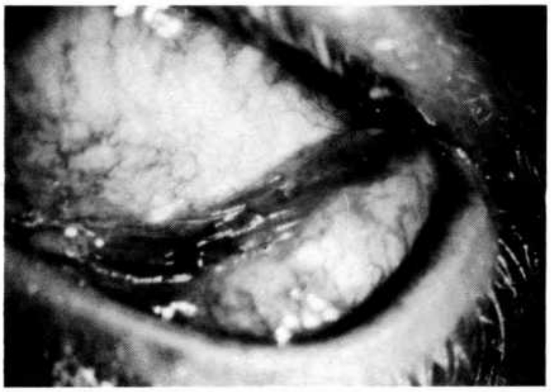

Fig. 1 *Clinical photograph of left lower eyelid and conjunctiva demonstrating the area of tumour.*

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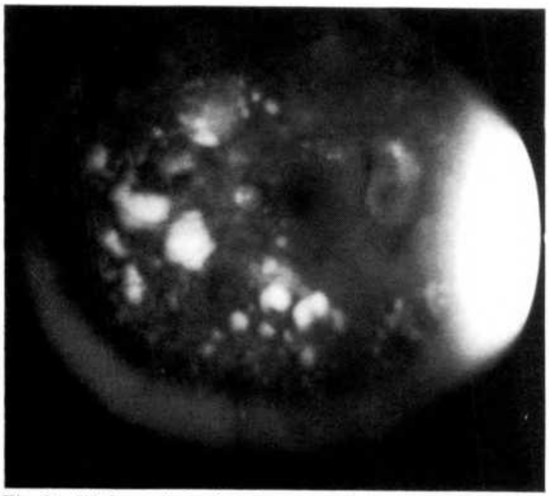

Fig. 2 *Wide angle fundus photograph of choroidal tumours in the left eye. There is an incidental temporal island of chorioretinal atrophy.*

and computed tomography (CT) scan of head and body were all negative.

When first seen at our service the patient's best corrected visual acuity was 6/5 in the right eye and 6/9 in the left. A firm, non-tender, 3×2 cm nodule was palpable beneath the left brow. A similar lesion measuring 1×1 cm involved the left palpebral and bulbar conjunctiva inferolaterally (Fig. 1). The intraocular pressure was 17 mmHg in the right eye and 11 in the left.

Biomicroscopy revealed normal anterior segments and aphakia in each eye. Vitreoretinal examination was normal in the right eye. In the left eye, however, multiple, slightly elevated yellow choroidal tumours ranging from1 to 6 mm in diameter were present in the posterior pole and pre-equatorial regions (Fig. 2). There was shallow subretinal fluid overlying some of the larger lesions. The optic disc was normal and the vitreous was clear. A preoperative physical examination gave normal findings except for slight cervical and inguinal lymphadenopathy.

It was decided to biopsy the large brow mass. At surgery an unencapsulated, grey tumour was encountered and a wedge biopsy specimen taken. Histological examination showed a tumour composed predominantly of rather uniform large lymphocytes, which diffusely infiltrated the soft adipose tissues and surrounding nerves and blood vessels (Fig. 3). The nuclei were clear. From the nucleoli, which were large and irregularly shaped, emanated chromatin strands, which condensed along the nuclear rim. There were scattered benign lymphocytes as well. The pathological diagnosis was large-cell lymphoma.

Further systemic examination revealed no additional evidence of lymphoma. Cyclic combination chemotherapy with cyclophosphamide, adriamycin, vincristine, and prednisone was begun, and all

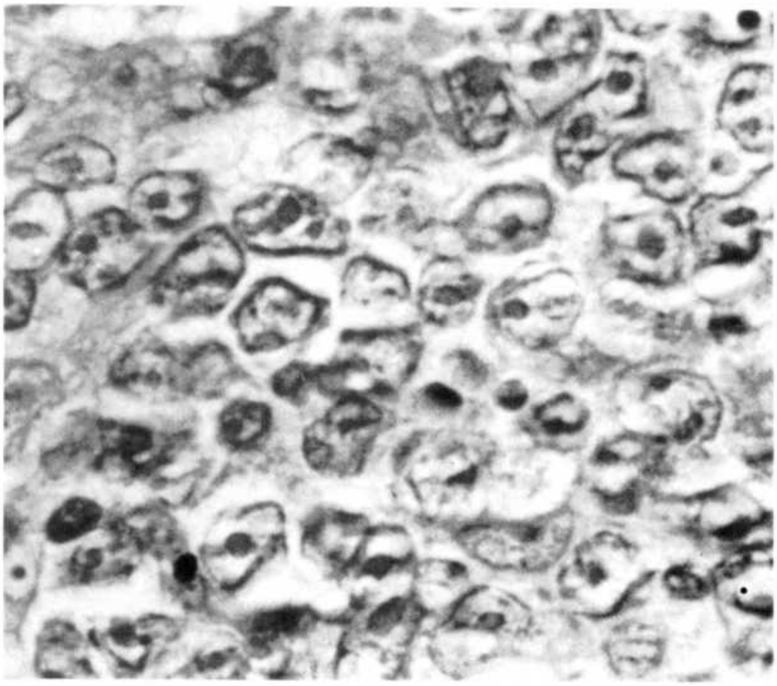

Fig. 3 *Photomicrograph of left brow biopsy specimen. Note lymphoid cells infiltrating normal tissue (Haematoxylin-eosin, ×250).*

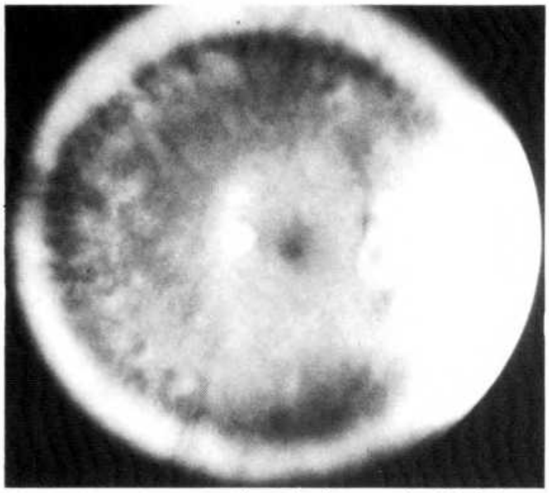

Fig. 4 *Post-treatment wide angle photograph of the left fundus. Note regression of tumours.*

known lesions including the lymphadenopathy regressed dramatically (Fig. 4). The visual acuity in the left eye improved to 6/5.

Six months later and only several weeks after the patient's sixth cycle of chemotherapy a new subcutaneous mass developed in the left breast. A slight swelling in the area of the right brow was also evident. A biopsy of the breast lesion was performed and a firm, walnut-sized nodule was removed. At microscopic examination a tumour composed of monomorphic lymphoid cells infiltrating the normal fat and connective tissue of the breast was identified. A review of the slides from the previous lid specimen showed the lesions to be histologically similar. The breast as well as the brow tumour also resolved on further chemotherapy. However, the patient returned in August 1984 with a 1×1 cm right lower lid nodule (Fig. 5). Additional chemotherapy is being undertaken.

Discussion

Large-cell lymphoma can be divided into two main presentation patterns. The first and most important to ophthalmologists is the intraocular-central nervous system (CNS) type. The combination of these two sites together 75% of the time clearly labels this as a distinct entity. There is only a 25% association with disseminated large cell lymphoma in this form.[4] Usually eye findings precede CNS clinical signs by an average of 21 months.[5,6] However, CNS disease rarely occurs before eye involvement. A posterior uveitis or a vitritis with or without chorioretinal involvement is the main feature.[7,8]

Diffuse systemic large-cell lymphoma is far commoner than the ocular-CNS form. Mainly a disease of lymph nodes, spleen, and bone marrow, it can also begin in the viscera or skin. This form is not usually associated with ophthalmic disease. However, when it occurs, orbital or ocular adnexal involvements is far more likely to be seen than intraocular lesions.[9,10] In addition, intraocular involvement here is more likely to be choroidal, as opposed to retinal or vitreal, as usually seen in the ocular-CNS form.[11] Proptosis and periorbital swelling are the typical presenting adnexal manifestations.[12]

Recent immunofluorescent techniques have detected immunoglobulins on the surface of the cells.[13-15] It now appears that large-cell lymphomas are derived mostly from B lymphocytes and rarely from T lymphocytes.

Our patient with systemic lymphoma is unusual in several respects. He represents one of the few cases

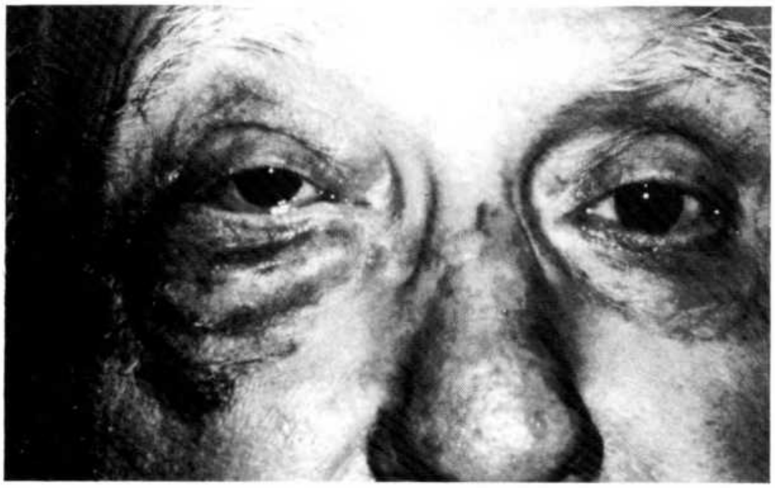

Fig. 5 *Clinical photograph of right lower lid nodule.*

of intraocular disease presenting in the systemic form of the malignancy. He is even more unusual in that his choroidal tumours became manifest early in the course of his illness and before any systemic signs or symptoms occurred. In addition he also had eyelid and conjunctival tumours, which prompted him to seek medical attention. The fact that his initial intraocular and periocular lesions were ipsilateral rather than contralateral may be coincidental, but the ocular-CNS form of large-cell lymphoma does tend to be ipsilateral.[16] However, it is also curious that our patient's later tumour sites involved the right periorbita.

Chemotherapy was used to good advantage in our patient. Both the original ophthalmic tumours as well as the later recurrences responded dramatically. Any future site will be similarly treated, with local radiotherapy held in reserve. Unfortunately there is no curative treatment for large-cell lymphoma, and the prognosis for our patient remains guarded.

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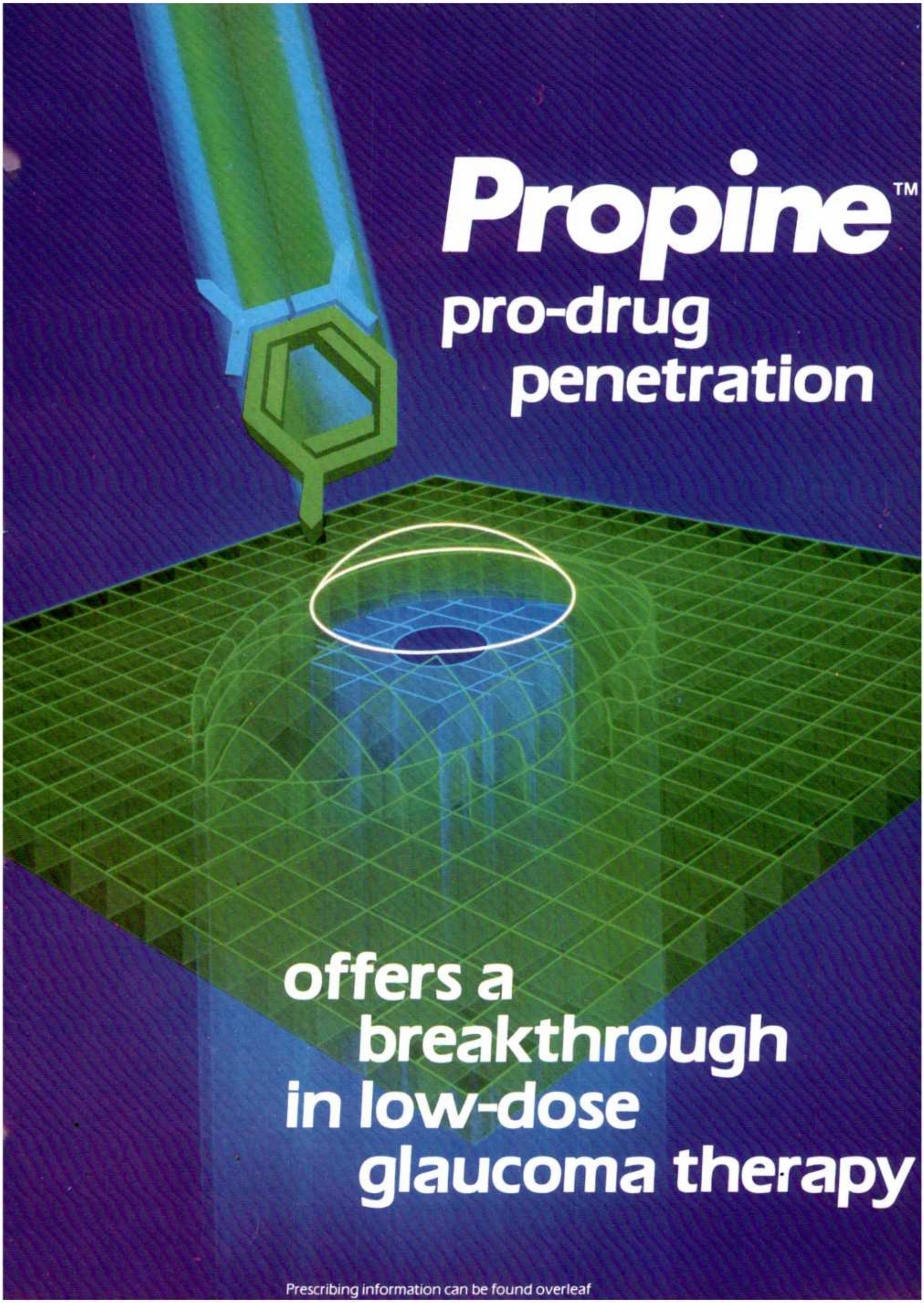

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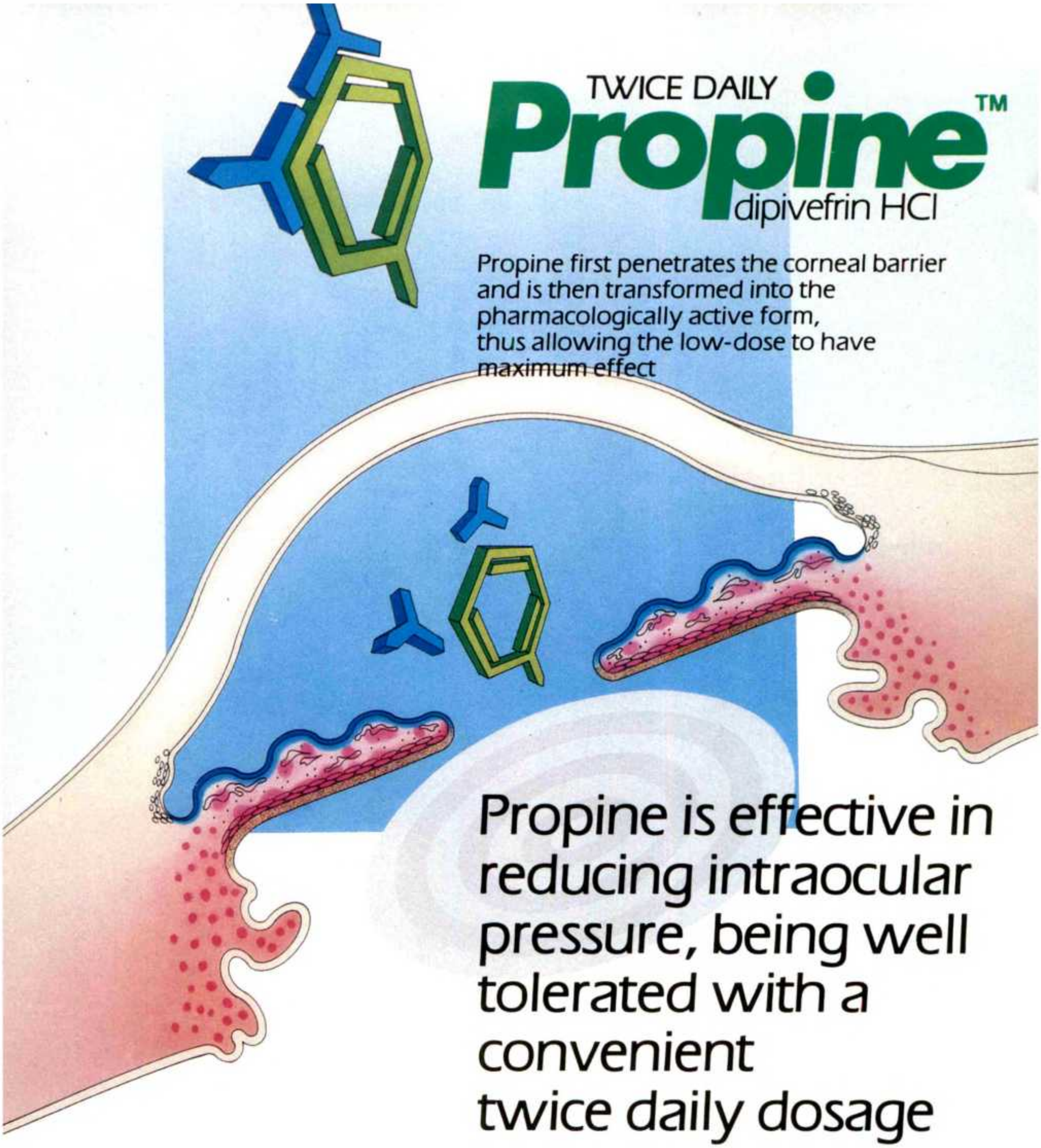

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One year in an eye casualty clinic

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SUMMARY A survey of patients visiting the eye casualty clinic of the Leicester Royal Infirmary was conducted during a one-year period. Demographic and clinical data were collected for 6576 patients. Data were recorded by both medical and clerical personnel during each patient visit. In addition to reporting the main demographic variables in the study, the most common diagnoses and occupations were analysed separately. The main diagnoses fell into two groups: trauma and acute infection/inflammation. The frequency of eye trauma in males was twice that in females. Trauma in adults was strongly influenced by occupation. Common occupations presenting with eye injury were press and machine tool operators, motor vehicle and aircraft mechanics, metal and sheet metal workers, construction and general labourers, electricians, welders, bus/lorry drivers and painter/decorators. Infections were in general distributed evenly throughout the population. The most common infection reported was acute conjunctivitis.

The cost to society of acute eye disease has led to increasing interest in the distribution of these diseases. Particular emphasis has been placed on eye trauma. Several studies have addressed the problem of eye trauma in the community[1-5] and in children in particular.[6-8] These studies generally included data which was collected from hospital records and whose focus was on severe injury. Surveys of ocular presentations of small numbers of patients to general emergency departments have also been conducted.[9 10] In most reports of eye casualty problems attention is generally directed towards management rather than occurrence of disease. In order to survey the broad range of eye casualty problems that require medical attention we initiated a project to evaluate an eye casualty clinic which is part of a general health care system serving a large community.

The study took place at the Eye Clinic of the Leicester Royal Infirmary (LRI), which has the only ophthalmology service in the Leicestershire Health Authority (LHA) and hence has a unique catchment population of eye disease. Of the approximately 835 000 inhabitants served by the Leicestershire Health Authority about 42% live in and around the city of Leicester. The eye casualty clinic is located within the general eye clinic and is the only eye casualty unit in the LHA.

In this paper we present summary statistics for several demographic and clinical variables of eye casualty patients seen at the LRI during a one-year period. We then looked further at the eye disease observed in the main occupational groups.

Materials and Methods

Data were obtained for 6987 patients visiting the eye casualty clinic of the LRI between 1 September 1981 and 31 August 1982. A set of variables which encompased both demographic and clinical data was collected at each patient's initial visit to the clinic. Variables included the following: hospital record number, visit date, consultant ophthalmologist, postal code, date of birth, country of birth, occupation (industry), ethnic group, religion, source of referral, diagnoses, and disposal. Data from return visits included the hospital record number, visit date, diagnoses, and disposal. Records for 6% of the patients (n=411) lacked all demographic data. The first visit for these patients had been recorded as a return visit, and return visit forms lacked the necessary demographic data. These patients were dropped from the study. The number of patients therefore remaining in the study was 6576.

The variables were categorised as follows. Diagnostic codes followed the International Classification of Diseases, 9th revision.[11] Classification of occupations followed that compiled by the Office of

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Population Censuses and Surveys[12] with the following additions: housewife, handicapped or disabled, child not in school, schoolchild, and student. The referrals used in this report were general practitioner, self-referral, general emergency department, and all others. The last category included optician directly, other specialty clinic, community medical officer, and outside referrals such as the Blind Society. Disposals were as follows: return to casualty clinic, admit to eye ward, admit to other ward, day care admission, surgical waiting list, refer to other consultant, blind registration, and discharge. 'Ethnic origins' were designated as Caucasian (Western), Indian/Pakistani, Negro, Oriental, and other. Religions were Christian, Jewish, Hindu, Moslem, Sikh, and other.

The data were first recorded on specially prepared patient visit forms which were filled out by the medical and clerical personnel during each visit. The data were then coded by a technician for input into the computer. The coded data were transferred to magnetic tape at the University of Leicester Computer Laboratory. The data tapes were analysed on the IBM 3081 computer at the Information Technology Service at Stanford University. By means of a program developed within the statistical package, Statistical Analysis System [SAS], the visit records were reorganised into patient records which included a summary of the data from the set of visit records for each patient (Chiapella AP, in preparation).

Out-of-range values in the data for these patients were either corrected or excluded from the statistical analyses. No more than 25 were found for any one variable and most variables had fewer than 10. The set of patient records was then analysed by procedures provided in SAS.

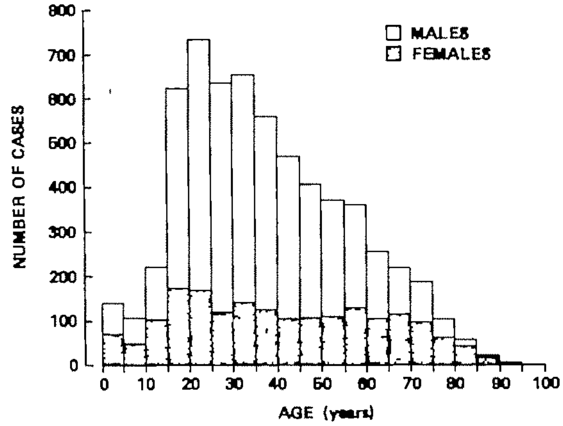

Fig. 1 *Age of casualty clinic patients. The age distribution of the patients is subdivided by sex.*

Results

DEMOGRAPHIC VARIABLES

Sex. 29% of the patients were female and 71% male.

Age. The median patient age was 23 years. The ages of the patients, subdivided by sex, are shown in Fig. 1.

Country of birth. 85% of the patients were born in England, 3·5% in India, 1·5% in Northern Ireland, 1·4% in Keyna, 1·3% in Scotland, 0·9% in Uganda, 0·9% in Great Britain (unspecified), 0·5% in Africa (unspecified), and <0·5% from any other country.

Table 1 *Most common occupations of patients attending the clinic**

Occupation	*Cases*	*Median age*	*Sex† (F/M)*	*Referral† (GP/self/other)*	*Main diagnosis groups‡ (ker[1]/acute conj[2]/ lid inflam[3]/injury[4]*
Press, machine toolsetter, operator	650	36	1/99	12/76/12	6/9/3/76
Schoolchild	412	13	35/65	40/45/15	6/19/13/50
Housewife	304	49	100/0	65/29/6	12/17/8/17
Clerk	222	41	64/36	45/44/11	8/27/11/29
Textile worker	205	46	61/39	45/40/15	13/20/7/29
Metal worker, machinist	189	33	1/99	12/71/17	4/8/4/77
Motor vehicle, aircraft mechanic	190	28	1/99	9/74/17	7/9/5/77
Construction	179	34	1/99	15/70/15	6/10/6/73
General labourer	168	39	2/98	15/59/26	8/10/4/71
Sheet metal worker	148	29	0/100	7/82/11	6/10/1/83
Electrician	130	32	1/99	12/72/16	7/9/3/80
Distribution manager	124	42	12/88	23/58/19	13/10/7/48
Bus, coach, lorry driver	123	38	5/95	26/62/12	7/13/7/72
Welder	116	38	3/97	9/82/9	6/5/3/84
Student	110	20	40/60	35/52/13	10/14/10/38
Child, not in school	103	2	50/50	40/42/18	2/35/16/39

*Includes 100 or more patients †Percentage of patients
‡Percentage of patients in this occupation carrying the following diagnoses: [1] Keratitis [2] Acute conjunctivitis
[3] Inflammation of the eyelids. [4] Injury.

Ethnic background. 90·3% were Caucasian (Western), 8·0% Indian or Pakistani, 1·3% black or African, 0·4% other.

Religion. 83·6% were Christian, 4·7% Hindu, 1·8% Sikh, 1·2% Moslem, and 8·7% other or unspecified.

Occupation. Sixteen occupations included 100 or more patients. The median age, sex ratio, source of referral, and main diagnoses for patients in these occupations are summarised in Table 1.

Postal code. Our data, which included patients' postal codes, are compared with catchment population data provided by the LHA. A map of the catchment area of the LHA is provided in Fig. 2 Postal codes LE1-LE5 (mainly the city of Leicester and nearby suburbs) provided 55% of the patients, LE6-LE9 (suburban areas) provided 32% of the patients, LE10-LE17 (the most outlying areas of the county) 10%, and the non-LE postal code areas less than 3% of the patients. The population data show that 41·6% of the resident population live in LE1-LE5, 26·6% in LE6-LE9 and LE10-LE17, and 5·2% live in non-LE postal code areas. It is therefore clear that the population in and around the city of Leicester utilises the casualty clinic considerably more than the population from outlying areas.

CLINICAL VARIABLES

Source of referral. 56% were self-referred, 30% were referred by the general practitioner, 8·6% came from the general emergency department, 1·3% from other specialty clinic (not LRI), 1·0% from their optician directly, 0·8% from the specialty clinic in the LRI, 0·2% were referred by community or school medical officer, and 2·1% came from all other sources.

Number of visits. 79% of the patients came for one visit to the casualty clinic, 15% for two visits, and 6% for more than two visits. Usually after three to four visits the patient was then discharged or referred to the general eye clinic.

Disposal. 78% were discharged, 32% were referred to the general eye clinic, 2% admitted to eye ward, 1% put on waiting list (for surgery), 0·7% referred to other consultants, and 0·2% were alloted to all the other disposals. This adds up to over 100%, since some of the patients contributed more than one disposition. Most of these were patients who, after discharge, returned to the casualty clinic and were then referred to the general eye clinic.

Diagnostic categories. The main diagnoses seen at the casualty clinic fell into two general categories: trauma and acute infection/inflammation. As a group, the patients in each of these categories differed from those in the other category with respect to several characteristics. An analysis of these patient groups is presented below.

Trauma was the leading cause of patient presentation to this casualty clinic, accounting for 52% of the patients attending. The main problems included in this group were corneal abrasion, foreign body on external eye, contusion of eye and adnexa, and burn confined to eye and adnexa. In the age range 5–15 years boys presented with eye trauma twice as often as girls. The patients above age 15 were mainly men,

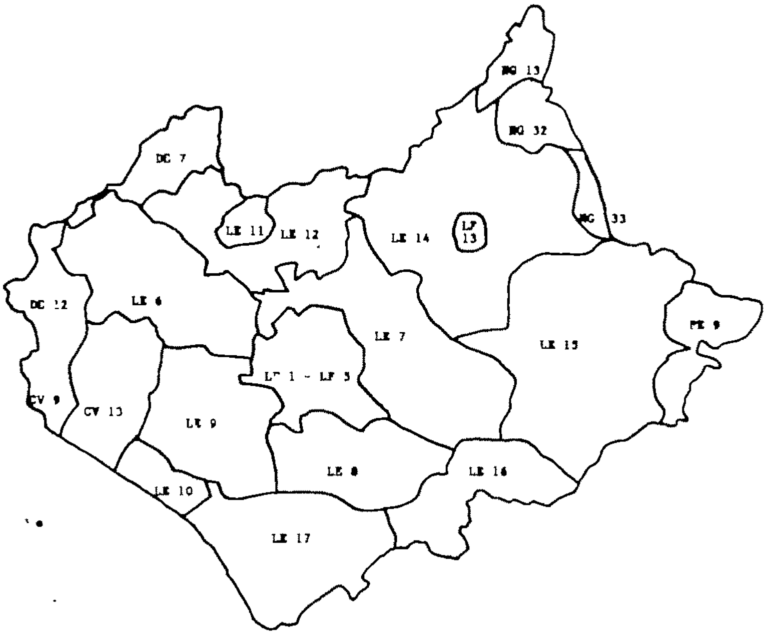

Fig. 2 *Map of catchment area of Leicestershire Health Authority showing postal codes.*

and in these patients the injuries were highly influenced by occupation. Over 70% of the patients with a diagnosis of trauma were self-referred. Table 2 presents a summary of the age, sex, and source of referral for the four most common trauma diagnoses. The majority of the patients with eye trauma came from relatively few occupations. We have identified 11 common occupations in which the risk of eye injury was high. 50% of the injury cases came from these 11 occupations, while only 35% of the casualty clinic patients fell into these occupational groups. For patients in these occupations the ratios of accidents to other eye casualty problems was much higher than those found in the remainder of the occupational groups. Table 3 summarises the types of injuries for patients in these 11 occupations.

The second most common diagnostic group into which the eye casualty patients fell was infection/inflammation, and it accounted for 29% of the patients attending. The male/female ratio in the various diagnoses included in this group ranged from 0·6 to 2·0. There were many more referrals by general practitioners for this group of patients than for the trauma patients. However, there is considerable variation between diagnoses. Those diagnoses which were mainly general practitioner referrals were keratitis, chalazion, herpes zoster ophthalmicus, and iridocyclitis. Those which were mainly self-referrals were superficial keratitis and conjunctival vascular disorders, for example subconjunctival haemorrhage. Those balanced between self-referral and general practitioner referral were scleritis/episcleritis, corneal ulcer, acute conjunctivitis, deep inflammation of eyelid, entropion and trichiasis of eyelid, blepharitis, and keratoconjunctivitis. A summary of these findings is presented in Table 4.

Discussion

The main source of emergency ophthalmic care for the population of Leicestershire is the eye casualty clinic located within the general eye clinic of the Leicester Royal Infirmary. This situation provided a unique opportunity to survey eye casualty problems in this diverse population for a one-year period.

On a per capita basis the inhabitants of Leicester utilised the casualty clinic more heavily than people living in outlying areas. There are several possible causes for this finding. (*a*) Drift to clinics located outside Leicestershire undoubtedly occurs from the outlying areas. (*b*) General practitioners working at great distances from the LRI may be more likely to treat rather than refer their patients. (*c*) Fewer prob-

Table 2 *Trauma patients*

Injury	*Cases*	*Median age*	*Sex* (F/M)*	*Source of referral* (GP/self/gen casualty clinic/other)*
Corneal abrasion	849	32	22/78	12/68/16/4
Foreign body	2106	32	8/92	7/80/9/4
Contusion	214	24	23/77	19/60/15/6
Burn	240	27	21/79	5/73/12/10

*Percentage of patients

Table 3 *Occupations presenting with eye injury*

Occupation	*Number of cases*				
	All injuries	*Burn*	*Contusion*	*Foreign body*	*Corneal abrasion*
Press, machine tool operators	494	13	13	425	64
Motor vehicle, aircraft mechanic	147	10	7	111	18
Metal worker	145	7	4	111	27
Construction	131	16	6	82	37
Sheet metal worker	124	3	3	108	12
Electrician	104	5	3	77	24
General labourer	120	6	5	79	34
Welder	97	9	3	72	18
Bus, coach, lorry driver	76	4	5	46	23
Others in processing	51	4	1	23	8
Painter and decorator	44	7	1	23	17

Note that the sum of cases in the four injury diagnoses may be more than 'all injury' cases. This is because a few patients had more than one diagnosis

Table 4 *Acute infection and inflammation. summary of most common diagnoses**

Diagnosis	*Cases*	*Median age*	*Sex† (F/M)*	*Referral† (self/GP/other)*
Acute conjunctivitis	626	33	44/56	38/50/12
Chalazion	246	33	52/48	65/28/7
Acute/subacute iridocyclitis	183	49	43/57	68/22/10
Corneal ulcer	140	45	33/67	53/38/9
Scleritis and episcleritis	122	34	53/47	53/36/11
Conjunctival vascular disorders	115	46	39/61	24/61/15
Superficial keratitis without conjunctivitis	100	30	38/62	31/55/14
Hordeolum and other deep inflammation of eyelid	82	30	43/57	46/41/13
Herpes zoster with ophthalmic complications	73	67	55/45	85/13/2
Interstitial and deep keratitis	65	47	42/58	56/26/18
Other and unspecified keratoconjunctivitis	66	55	61/39	60/26/14
Entropion and trichiasis of eyelid	60	45	44/56	44/45/11
Blepharitis	57	39	52/48	50/43/7

*Cases with trauma have been deleted from this Table
†Percentage of patients

lems, especially injury, may occur in rural areas. (*d*) The different distribution of occupations between city and rural areas may account for these differences. (*e*) Finally, attitudes held by people in these areas may lead to differences in utilisation of medical resources. Patients in rural areas may not wish to come into Leicester because of the inconvenience, loss of earning, difficulty in transport, and also because they may have a much higher threshold before they seek professional medical help.

A typical patient coming to the eye casualty clinic during the study year was a man of working age with an eye injury. He was self-referred and came for one visit only. He was likely to be in one of several occupations which appeared to be at risk for eye injury. Although data are not available on the incidence of injury at work versus that outside work, it seems reasonable to assume that most of the injuries occurred at work, since the patients presented to the eye casualty clinic during normal working hours. This presumed high rate of job-related injuries would indicate that these workers are not being adequately protected by eye shielding devices. This could be due to inadequate devices, a lack in supplying of devices, and/or the improper use of devices when provided. The second possibility is that these workers, when not at work, sustain injuries more often than others. They may involve themselves in more risky activities, such as sports or motor car and house repair. Identifying the specific causes of the high rate of injuries deserves further attention.

In this study boys presented with eye injury twice as often as girls. This finding is in the same direction as those presented by other investigators for injuries in children.[5-8] The ratio, 2:1, is lower than that noted by other authors, who have reported ratios of 3:1 and higher.[5-8] In contrast to the other studies the patients in our study were not admitted to hospital. This may indicate that the ratio of eye injury in boys versus girls may be smaller for less severe injury than for those injuries requiring admission to hospital.

Although this study has concentrated mainly on summarising data on the patients attending the eye casualty clinic over a one-year period, it has raised the possibility of providing further epidemiological information, especially with regard to occupations at risk for specific ocular injury and the possibility of seasonal variation in emergency ophthalmological disease.

The collection of data is continuing, analysis of which should throw better light on utilisation of ophthalmic emergency facilities by this population.

The authors thank the consultants, junior staff, and clerical staff of the Eye Clinic of the Leicester Royal Infirmary for their participation and co-operation during this study Particular appreciation is given to Marcus Lesmak for his enormous contributions Also thanks to Dr J Jones, who provided the population statistics of the Leicestershire Health Authority.

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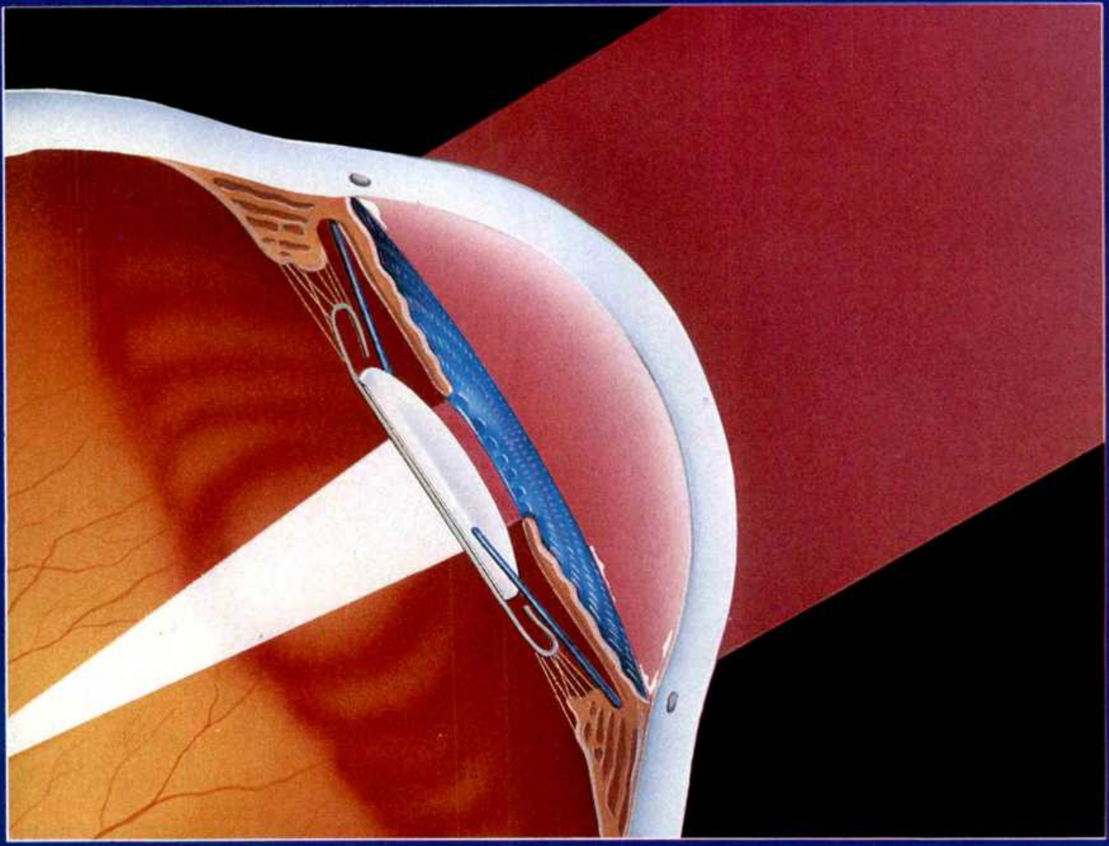

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Book reviews

Metipranolol. Pharmacology of Beta-blocking Agents and Use of Metipranolol in Ophthalmology. Edited by H-J Merté. Pp. 170. DM.68·00. Springer-Verlag: Wien. 1984.

This booklet reproduces the papers presented at the first Metipranolol Symposium held in Berlin in January 1983 to mark the launch of a new topical beta blocker for glaucoma treatment The original German edition was published late the same year. and this review is of the English edition published in 1984

The symposium has 16 listed speakers; all are German The papers presented included three introductory papers on the principles of pharmacology and drug trials, two papers on short-term clinical trials using metipranolol, three papers comparing metipranolol and timolol, and two 'long-term' studies of metipranolol drops. It would appear that metipranolol is a non-cardioselective beta blocker without intrinsic sympathomimetic activity. It is marketed in concentrations of 0·3% and 0·6% and is administered twice daily. The 0·3% is equally potent with timolol 0·25% The studies in this book show that a 30% reduction in intraocular pressure can be expected in the short term, but there is a falling off of this hypotensive effect to 20–25% after four weeks of treatment It would appear that the drops produce a greater incidence of ocular irritation than timolol, although the reason for this was not clear to the authors reporting it

Metipranolol, on the basis of the information included in this booklet, would appear to be an alternative beta blocker to timolol without clear advantages over the latter drug. The booklet itself would be of interest to ophthalmologists with a subspecialty interest in glaucoma and/or ocular pharmacology and therapeutics. ROGER A HITCHINGS

Molecular and Cellular Basis of Visual Acuity. Cell and Developmental Biology of the Eye. Edited by S Robert Hilfer and Joel B Sheffield. Pp. 184. DM 98·00. Springer-Verlag: Berlin. 1984.

I usually think that symposium issues serve no other function than to provide a publishing medium for otherwise unpublishable papers Nothing is more infuriating than picking up a volume with an extremely exciting title only to find a number of dissociated and discordant papers of varying scientific content and integrity. It is therefore a pleasant surprise to discover this series on the cell and developmental biology of the eye. The present volume is the third, and it certainly keeps up with its predecessors in terms of scientific merit of its component papers. The editors have done an extremely good job in choosing experts in their field and then in guiding them in such a way that the papers form a cohesive unit.

The molecular and cellular basis of visual acuity does precisely what its title suggests. It considers the cellular and molecular mechanisms underlying visual acuity and its development It is particularly helpful to have a number of modern reviews of both chemistry and anatomy and the interrelationships between these two fields This collection of review articles also provides a wealth of references for the reader who is new to the field If the book has a failing, it is that it does not cover the changes in visual acuity with the increase in age However, I am sure that this area will be addressed in a future symposium issue.

In summary, I commend the editors and the authors for producing an extremely useful and timely book.
JOHN MARSHALL

ACTA 24th International Congress of Ophthalmology, San Francisco, 1982. Vols. 1 and 2 Edited by Paul Henkind. Pp. 1379. £142·50. Harper and Row: London. 1984.

This work in two volumes comprises 1274 pages of original papers, plus sections on the regulation of instruments and devices, the International Agency for the Prevention of Blindness, and the International Committee for Teaching and Postgraduate Education. In the preliminary addenda of volume 1 are some notes on various matters including the minutes of the meeting of the International Federation of Ophthalmological Societies, where the reports of various committees were considered. There is also a list of the names of the approximately 10 000 ophthalmologists attending the congress

The scientific papers are arranged in sections by subjects, starting with genetic eye diseases and congenital abnormalities followed by ultrasound perimetry, trachoma, cornea, cataract and anterior segment surgery, retina and vitreous, uveitis, glaucoma, diabetes, other systemic diseases, strabismus, tumours and plastic surgery, injuries, contact lenses, optics and refraction, and electrophysiology and visual psychophysics. The book is evidently the result of much hard work by its editorial chief To assemble this enormous mass of literary material from such a diversity of sources and from such a large number of individual ophthalmologists in so short a time and to weld it into two very presentable volumes is a marvellous achievement Paul Henkind and his editorial committee are much to be congratulated

It is appropriate that the first paper in the volume should be a major contribution from the late Jules François: a fitting last offering to the international ophthalmological community. Although we are all sad to have lost Jules it was good that he lived to enjoy the largest ophthalmological congress ever held. REDMOND SMITH

Documenta Ophthalmologica Proceedings Series 39. Colour Vision Deficiencies VII. Proceedings of the International Symposium, Geneva 1983. Edited by G Verriest. Pp. 424. £51·00. Junk: The Hague. 1984.

As was only to be expected, the vigorous momentum of the subject of acquired chromatic defects could not be kept up. It now occupies a quarter of the latest volume of this remarkable series. Far from being a complaint, this change of emphasis is mentioned in order to stress that the width of interest is much expanded. A section on new aspects of fundamentals is followed by practical matters, with special attention being given to clinical applications. New data are presented on both congenital and acquired defects A remarkable paper on the microspectrophotometry and sensory data on the *same* deuteranopic eye is a pointer for the future: we are well on the way towards distinguishing between retinal and central processing mechanisms without having recourse to speculation.

In *Fair Blows the Wind for France* H E Bates describes how, on having parachuted down, a dazed pilot experienced two bouts of loss of colour vision When I asked the author about his sources for the existence of this symptom, he told me that he had invented it Were he alive he would find the authority for his invention at the end of this book

ROBERT WEALE

Retinal Detachment Surgery: Strategy and Tactics. By JAMES S SCHUTZ. Pp. 140. £15·00. Chapman and Hall: London. 1984.

This book has been written with the intention of providing a surgical guide to retinal detachment repair. It has been carefully and thoughtfully written as a step-by-step guide to retinal detachment surgery The reader is taken through a logical sequence of events on the preparation of the patient through preoperative and operative considerations and postoperative problems.

The book is illustrated by several line diagrams to help to illustrate the various points made in the text. The author's views are clearly presented, and in the main the text is very readable. The problem in a small book on retinal detachment surgery is always that of knowing what to include and what to leave out. Thus I found the chapter on surgical preparation and surgical exposure somewhat irritating (for example, the reasonable assumption that the lights should be properly adjusted prior to surgery) One would expect to find points of disagreement in several aspects of the clinical management of the cases, thus I did not find myself in agreement with the points made about barrage cryotherapy or bed rest after cryotherapy Surely the main point of injecting intraocular air at the time of retinal detachment surgery for retinal detachments not complicated by periretinal fibrosis is simply to push the retinal hole back up against the pigment epithelium, which will then allow easy sequential cryotherapy and buckling. New breaks occurring on the posterior slopes of scleral buckles are very rare In the planning of the operation, it might also be nice to have a slightly more comprehensive explanation of the modern concepts of vitreoretinal traction. It is an easy expression to use, and the correct application of these concepts is fundamental to the planning of retinal detachment surgery

I thoroughly enjoyed reading the book and I strongly recommend it to registrars in training. I also feel that the consultants, for whom they work will acquire valuable knowledge from its text

A CHIGNELL

Clinical Ocular Pharmacology. By JIMMY D BARTLETT AND SIRET D JAANUS Pp. 978. £80·00. Butterworths: Sevenoaks, Kent. 1984.

The first surprise on reading this, a large multiauthor book, is to find that it has been written by American opticians with only one small chapter from a non-ophthalmic medical contributor In recent years there has been a considerable expansion by opticians in the USA into not only diagnostic but also therapeutic ophthalmology, and both the foreword and the preface make it clear that the aim of the book is principally to advance this aim The second surprise is to find that the title is largely a misnomer, as the book contains relatively little pharmacology but instead has large sections on diagnosis and management of various conditions; one is surprised to find conditions such as keratoconus and pterygia in a pharmacological text. The book is therefore more of a clinical textbook for opticians, though the editors naturally feel it should have a wider acceptance

I found the text to be written at a low to middle postgraduate standard. The book lacks sufficient detail to be authoritative, and there is a heavy concentration on American trade pharmaceutical preparations. The absence of medical authorship often becomes apparent, and I was frequently left with an uneasy feeling that some material, while not being inaccurate, was not completely correct either. Only minimal attention is given to the pharmokinetics of individual drugs, ocular levels, penetration, and routes of delivery, and this is the book's major failure.

I cannot comment on whether opticians will find this a useful book or not, but ophthalmologists will find it disappointing and that their needs are served better elsewhere

D J SPALTON

The Apocrine Glands and the Breast. By MARSHALL B L CRAIGMYLE. Pp. 82. £24·00. John Wiley: Chichester, Sussex. 1984.

This is a short, very readable book on the apocrine glands and the breast. It is divided into two sections, one dealing with the apocrine glands, that is, the glands of Moll, and one with the breast. Both sections are well written with an extensive bibliography at the end of each chapter.

A detailed description of the development, growth, and anatomy, both histological and gross, of each topic is presented The section on apocrine glands contrasts them with eccrine glands and clearly differentiates the two types The applied clinical content of the book is weak, and its expansion would perhaps have added more to the book All in all this is a concise easily read book that can be read in a short time and would be of interest to those who deal with skin tumours and diseases of the skin.

L H ALLEN

Note

New Orleans Academy

The New Orleans Academy of Ophthalmology will hold its 35th annual symposium on the cornea, refractive surgery, and contact lens on 8–11 March 1986. Details from Emily Busby, Executive Secretary, Eye, Ear, Nose and Throat Hospital, 145 Elk Place, Room 203, New Orleans, LA 70112, USA.

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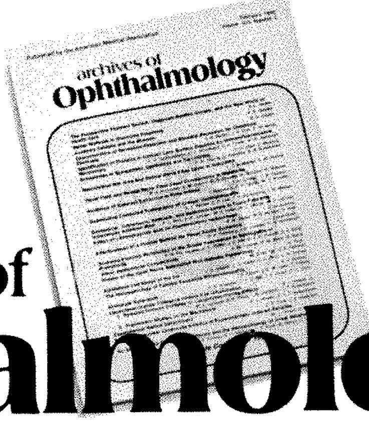

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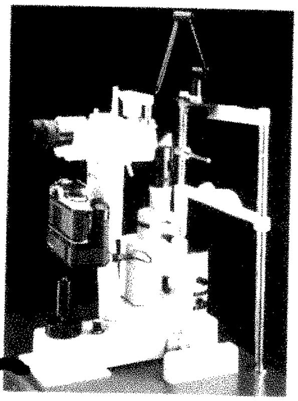

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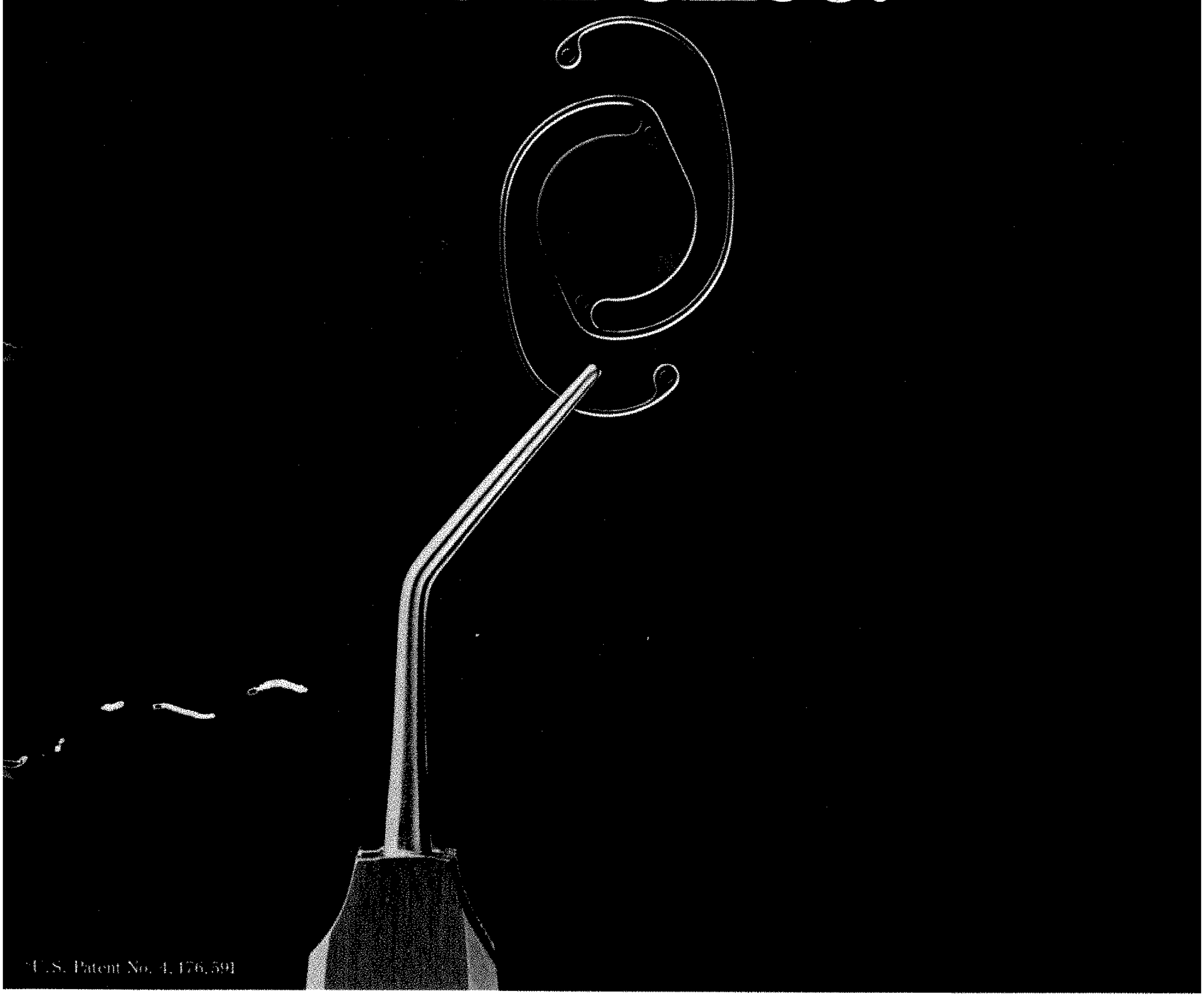

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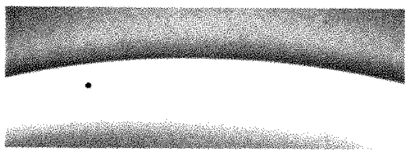

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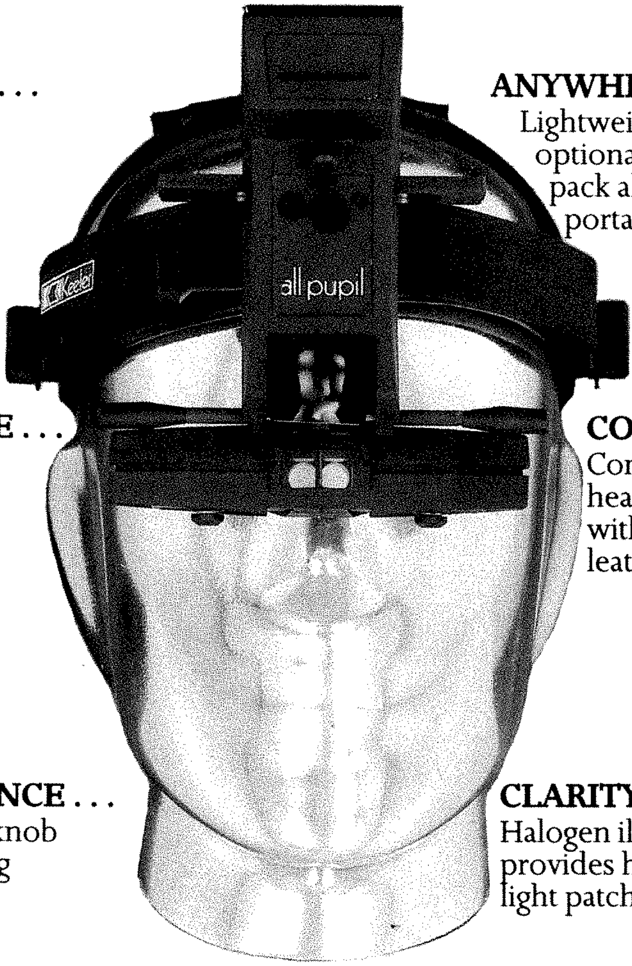

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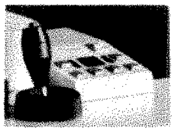

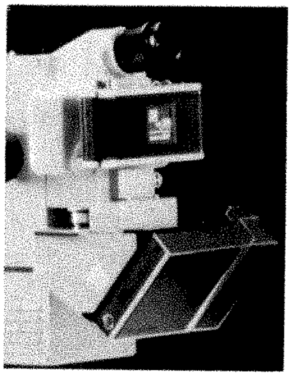

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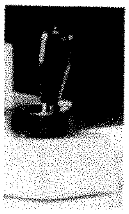

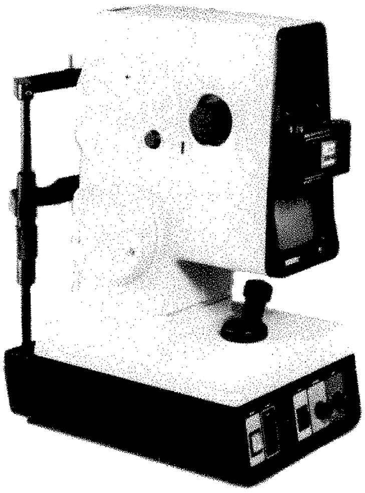

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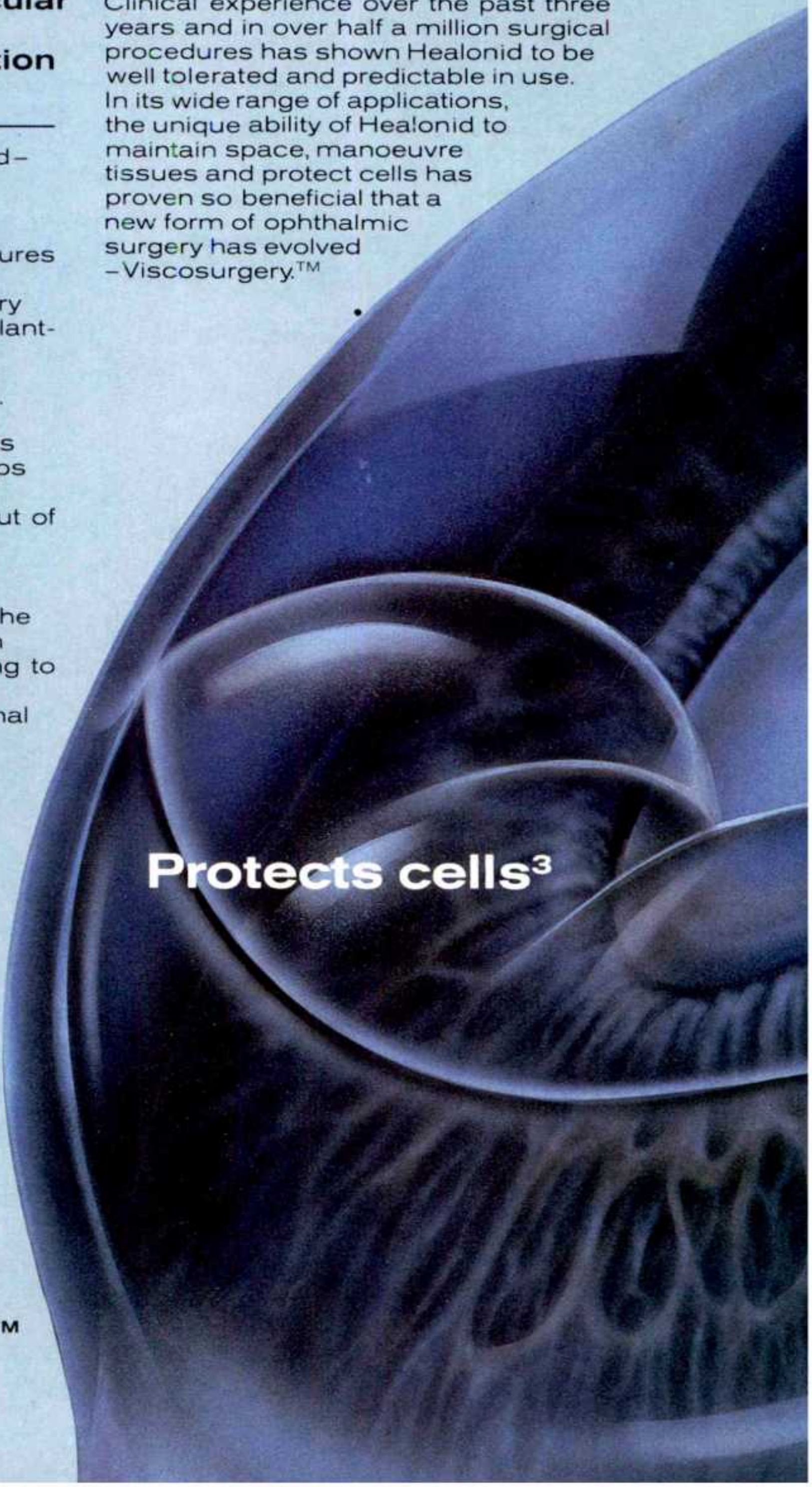

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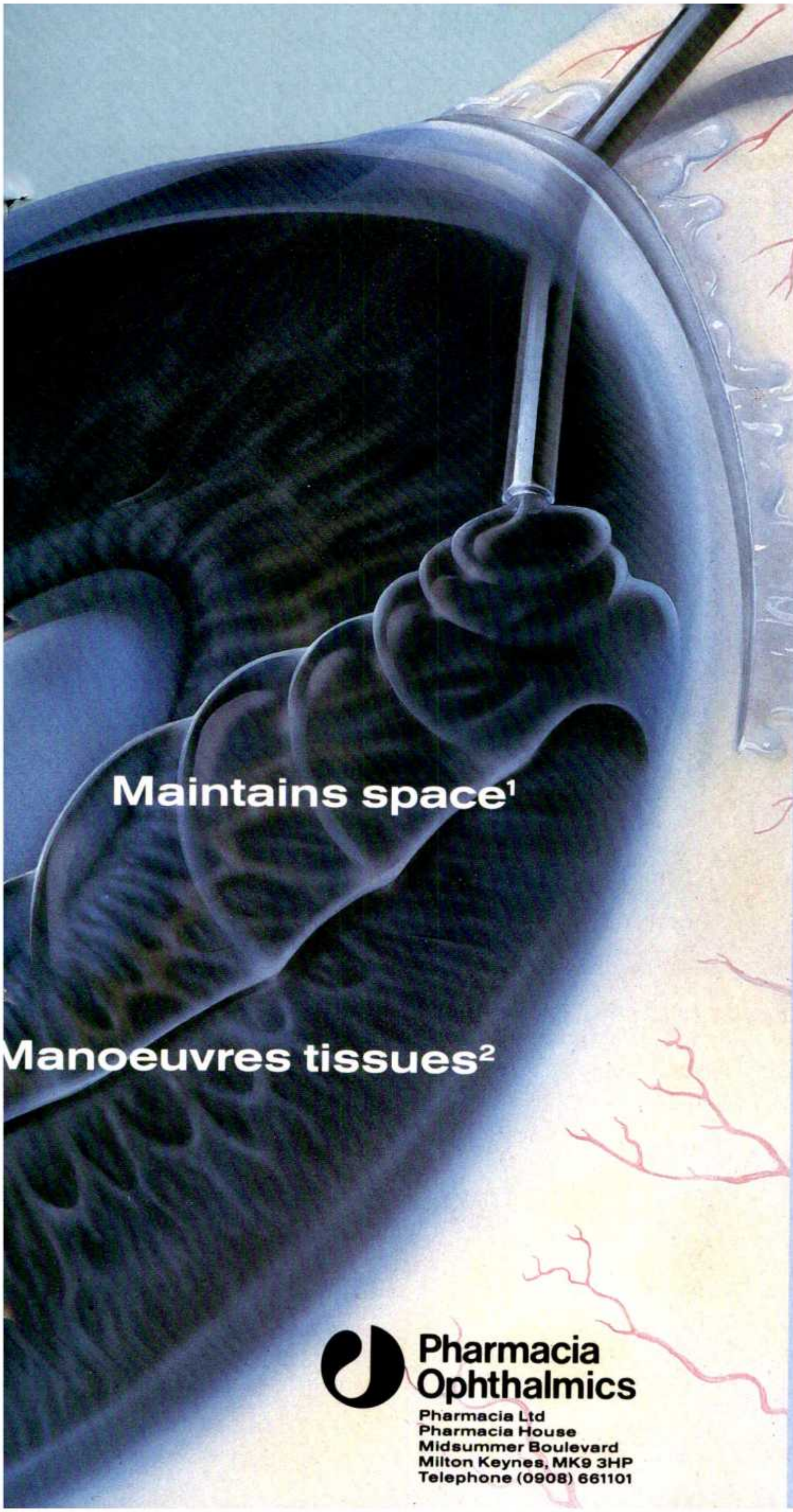

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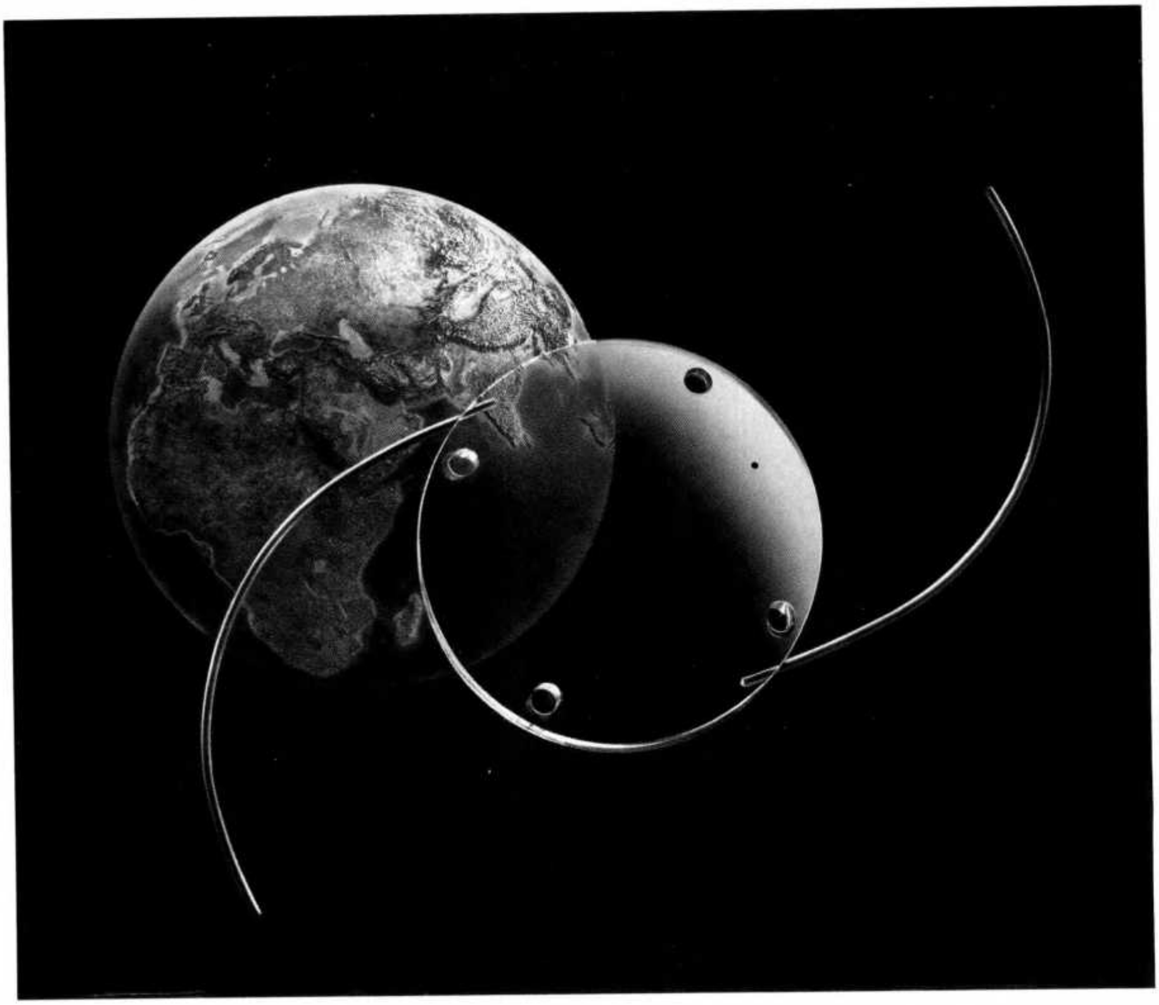

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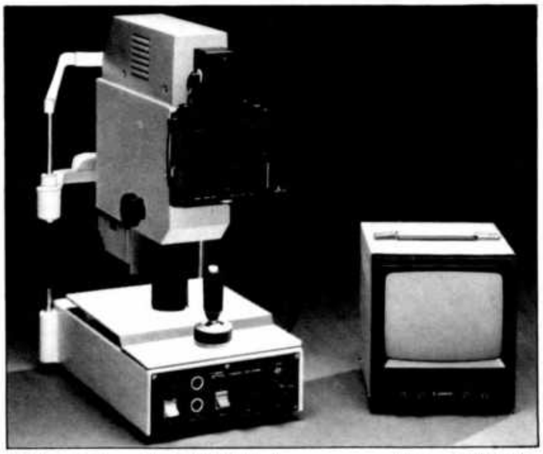

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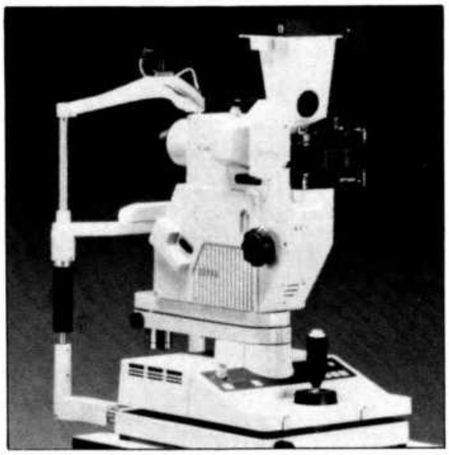

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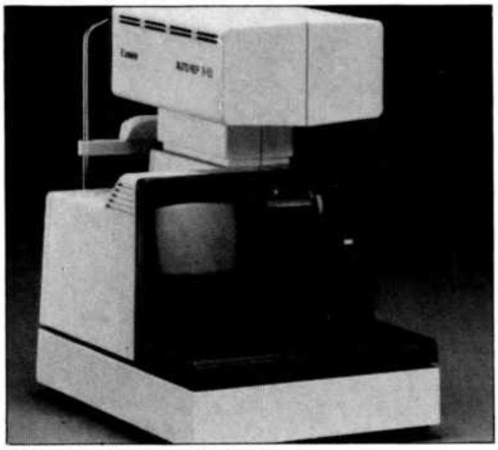

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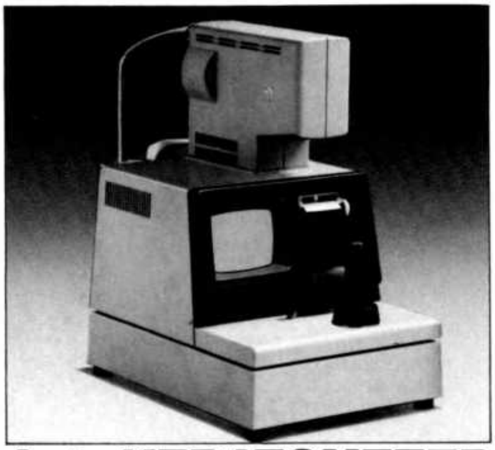

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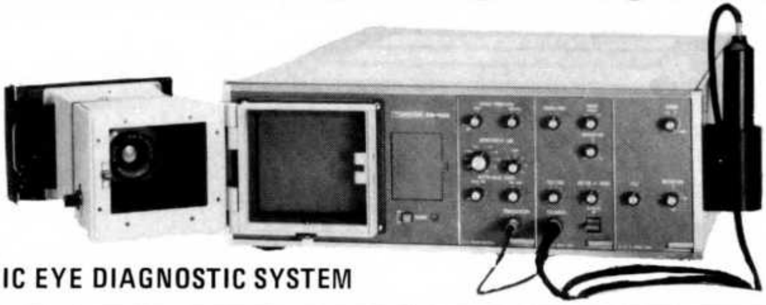

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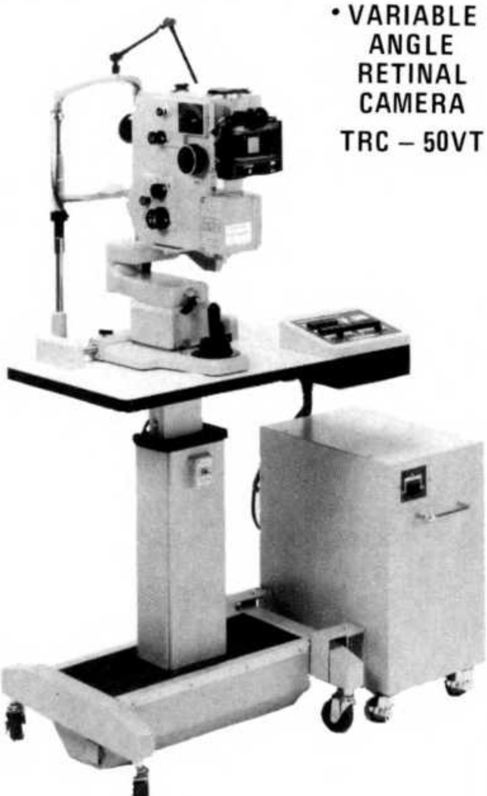

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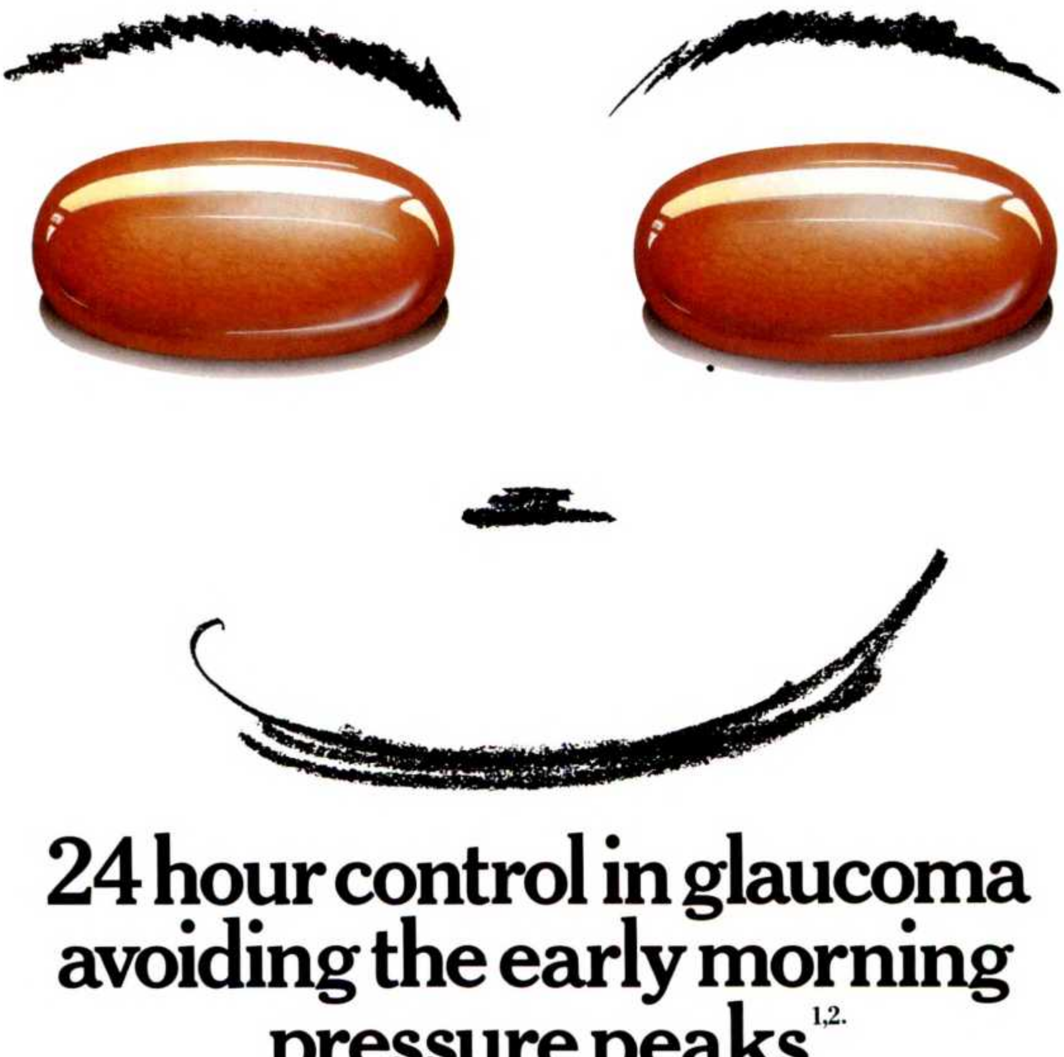

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British Journal of Ophthalmology, 1985, **69**, 873

Editorial: Are their spectacles really necessary?

In a study described in this issue Dr Jane Stewart-Brown reports that 11% of a group of 13 800 children born in one week in 1970 had been prescribed spectacles by the time they were 10 years old—about 1475 in all. Of these children 20% had no impairment of visual acuity, and a further 15% showed only minimal visual deficit. Thus about 516 children appeared to have been prescribed spectacles for no apparent reason. If these figures are extrapolated to 1 year, we have a total of 25 900.

It is easy to jump to the conclusion that many of the prescriptions had been unnecessary, but this would be unfair without more information than is provided by figures indicating visual acuities only. We need to know especially how many of these children were squinters, and the study does not tell us this, though squinting is alluded to. However, if we assume that the incidence of strabismus with an accommodative basis was, say, 2% in the whole population studied, and if we assume that half of such children had normal or near normal acuity, we arrive at a figure of 138 children, leaving 378 still with unexplained spectacles. If we make a generous allowance of, say, another 100 cases in which the measurement of visual acuity was inexpertly done or wrongly recorded, we are still left with 278 children or 14 456 per annum in the 'Why spectacles?' category.

Now if these children had normal visual acuities and were not squinters, they must have been given spectacles because of some other sign or symptom. The first symptom that springs to mind is headache, and indeed there is evidence in the report that a considerable number of children had been prescribed spectacles for that reason. There are of course many other reasons why a parent or teacher might think the child under his or her care could need spectacles, for example, peering closely at print or the TV, screwing the eyes up or blinking excessively, styes or blepharitis, failure to make good academic progress, and so forth.

With these points in mind it might be appropriate to consider the medical implications. With the possible exception of squint, there is little evidence that spectacles are of any use except to improve visual acuity: that is their function par excellence. One hears and reads a good deal about 'eye care' and the like, as though spectacles conferred some sort of benison on our eyes—but this of course is fanciful. The fact of the matter is that if we have the right glasses we get the best vision but if we have the wrong ones our acuity is impaired. There is really little more to it than that.

However, if glasses are to be used for what are apparently medical reasons, for example for the relief of headaches, is it desirable that they should be prescribed for this purpose outside medical supervision? It is true that we have no information from the present paper about the identity of the prescribers, but if we assume that the proportions conform to the national average, it would be likely that 80 to 90% of the prescriptions have been issued by non-medically qualified persons.

Opticians are under an obligation to refer persons to a registered medical practitioner if it 'appears' that they are suffering from a disease of the eye. The wording of the Act is vague, since it does not exhort the optician to examine the eye, and this 'appearance' that the patient might be suffering from something may be seen only incidentally in the course of 'testing the sight,' which seems to mean carrying out a refraction. Furthermore the Act leaves out completely the possibility that the person might be suffering from disease of some other part of the body, for example the brain.

The practice of refraction, consisting as it does of the determination of what lenses are required for best vision, has little or no medical content in itself. However, if the person doing the refraction is also carrying out the primary consultation (as distinct from a refractionist working in, say, an outpatient team) the subject regards the consultation as something akin to a medical examination, and there is a natural inclination for the refractionist to regard the 'subject' as a 'patient.' Thus what begins as a simple task—a refraction—is converted into a pseudomedical event. It is only a short step further for prescriptions to be given for non-optical reasons, and it is this aspect of refraction work, when carried out by non-medically qualified persons, that we find a little disturbing.

There is of course nothing in law to prevent an unqualified person from giving medical advice. Paradoxically, however, there is a law against persons not appropriately registered from prescribing spectacles or even testing sight, and we would therefore hope that, if the opticians are to continue to enjoy their unusually specific measure of protection, they would reciprocate by confining their prescribing to spectacles that are required for purely optical reasons.

RJHS

British Journal of Ophthalmology, 1985, **69**, 874–880

Spectacle prescribing among 10-year-old children

SARAH STEWART-BROWN

From the Department of Child Health, University of Bristol

SUMMARY Between 10 and 12% of the 10-year-old children in the 1970 national birth cohort were prescribed a pair of spectacles. One-fifth of these childen had no impairment of visual acuity and a further 15-20% had only minimal visual defects. Only two-thirds of children with spectacles could produce them when asked to do so at the survey school medical examination; this was particularly common among those in the lower social classes and among children who had no detectable impairment. The information presented in this paper combined with that from earlier national birth cohort studies suggests that overprescribing of spectacles to school children is very common. The financial implications of this overprescribing are discussed.

Since Roger Bacon discovered spectacles in the thirteenth century they have provided such unequivocal benefit to so many people with very poor vision that therapeutic trials to test their value would seem to be inappropriate. However, in recent years spectacles have been widely prescribed to people with relatively slight visual impairments; this is particularly so among children. The benefit to the latter from wearing spectacles is far from striking, but trials to test their value have not been proposed.

A recent publication from the 1958 birth cohort[1] presented data showing that as many as 18% of adolescents had been prescribed spectacles but that up to a quarter of this group had perfect or nearly perfect visual acuity. The paper called for further investigation into the criteria on which spectacles are prescribed.

In this study spectacle prescribing has been investigated among the children of the 1970 birth cohort. The aim was to establish how many 10-year-old children had been prescribed spectacles, to estimate the degree of visual impairment among children with spectacles, and to investigate whether factors other than impairment of vision influenced which children received spectacles.

Materials and methods

The data from this study were collected in the most recent survey of the 1970 birth cohort, which took place in 1980, when the children were 10 years old. The study began with a survey of all infants born during the week 7–11 April 1970 throughout the United Kingdom. Children living in Northern Ireland were excluded from the 1980 study. The 1980 survey included a parental interview conducted by a health visitor, a questionnaire which was completed by the child's school doctor after a thorough medical examination, and a self-administered questionnaire completed by the child's mother or the person who was mainly responsible for the child's care.

During the parental interview the parent(s) were asked whether the child wore glasses. The father's occupation and the child's home address was recorded. The former was classified according to the Registrar-General's Classification of Occupations[2] and the latter was grouped by standard region.[3]

The self-administered questionnaire included a question on whether the child experienced headaches. The responses were grouped into three categories: more often than once a week, less often than once a week but more often than once a month, and less often than once a month.

During the medical examination the doctor inquired whether glasses or contact lenses had been prescribed for current use and tested the child's distant and near visual acuity without glasses. Responses to the inquiry and results from the tests were recorded together with many other items of information. In the medical examination visual acuity tests were carried out under conditions similar to those in

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Table 1 *Categories of visual defect*

Description of defect	*Visual acuity*				*Predominant diagnostic category*
	Distant		*Near*		
No defect	6/6	6/6	6	6	Perfect vision
Bilateral minimal distant defect	6/9	≤6/9*	6	6	Bilateral myopia of increasing severity
Bilateral mild distant defect	≤6/12≥6/18	≤6/12*	6	6	
Bilateral marked distant defect	≤6/24	≤6/24*	6	6	
Unilateral distant defect	≤6/9	6/6	6	6	Unilateral myopia
Bilateral near defect	6/6	6/6	≤9	≤9	Mild and moderate hypermetropia
Unilateral near defect	6/6	6/6	≤9	6	Unilateral hypermetropia
Unilateral mild mixed defect†	≤6/9≥6/18	6/6	≤9	6	Amylyopia of increasing severity
Unilateral marked mixed defect†	≤6/24	≥6/9	≤9	≥9	
Bilateral mild mixed defect†	≤6/9≥6/18	≤6/9*	≤9	≤6	No predominant diagnostic category
Bilateral marked mixed defect†	≤6/24	≤6/24*	≤9	≤6	
	(≤worse than/≥better than)				

*Where visual acuity differs between the two eyes, defects have been classified to the level of distant visual acuity in the better eye
†Mixed defects are those in which both near and far visual acuity is affected.

which children are routinely screened in clinics and schools. Instructions were given with the questionnaire to test the child's distant vision with a Snellen chart, if available, by standing the child in a good light 20 ft (6 m) from the chart and covering first one eye and then the other. If no Snellen chart was available and an alternative was used, the type of chart was recorded. Near vision was tested with a Sheridan-Gardiner near vision chart which was provided with the questionnaire.[4] Instructions were given to hold this chart at a comfortable distance not more than 10 inches (25 cm) from the eye in a good light, and to test each eye separately. Gradations on the Sheridan-Gardiner chart range from 6 (perfect near visual acuity) to worse than 60.

Children with less than perfect visual acuity (6/6, 6/6 on distant vision, and 6,6 on near) were classified into 10 different categories. These are set out in Table 1. The categories were chosen, first, in order to be able to identify the large number of children with very minor or unilateral visual defects and, secondly, to be able to categorise children with defects to whom it was possible to attach a probable diagnosis.

The statistical significance of the findings was tested by the χ^2 test.

RESPONSE RATE

Parental interviews were completed for 13 782 children and medical questionnaires on 13 723; 13 681 self-administered questionnaires were completed by the mother. A total of 13 871 children participated in one or other aspect of the health survey. This represents an estimated 86·7% of the original birth cohort. Satisfactory visual acuity data were obtained on 12 853 children. For the remainder tests were either inadequately conducted or not carried out at all. There is a slight social class bias among the children for whom adequate tests were obtained, namely, 94·0% of social class I children as opposed to 90·5% of social class V. 91% of the moderately educationally subnormal ESN(M) children in the cohort completed the acuity tests but only 19·5% of those classified severely educationally subnormal ESN(S). Information on spectacle prescribing was obtained from either parent or doctor or both for all but 115 children.

Each series of analyses was carried out with the full complement of children for whom data were available.

Results

Doctors reported that 10·7% of the cohort children had been prescribed glasses or contact lenses. But the parents of 107 of these 1475 children responded negatively to the question, does your child wear glasses? Parents reported that 10·9% of children wore glasses, but for 135 of these children doctors said that no spectacles or lenses had been prescribed (Table 2).

The use of contact lenses, about which only doctors were asked, could not have been responsible for this discrepancy, since only 11 children in the cohort had been prescribed lenses by this age. The wording of the two questions about glasses may have accounted for some of the difference; not all children who had been prescribed spectacles would be expected to wear them. The medical examination and the parental interview were not completed at exactly the same time, so it is also possible that some children received a prescription for spectacles in the period between these two parts of the survey.

Whatever the cause, some degree of uncertainty must be taken into account in describing the data.

Table 2 *Spectacle prescribing in the 1970 birth cohort (n=13 756)*

	Children with spectacles	
	%	Number
Spectacles brought to medical examination*	7·1	980
Spectacles not brought to medical examination	4·6	630
Parents and doctor agree child has spectacles*	2·8	388
Only parents say child has spectacles†	1·0	135
Only doctor says child has spectacles†	0·8	107
Total: all children who may have been prescribed spectacles	11·7	1610

*These two groups are together referred to as definite spectacle prescriptions

†These groups are together referred to as possible spectacle prescriptions.

The group of children about whom there is disagreement between parents and doctors have therefore been included in all tables as having possible spectacle prescriptions.

Of all the children who may have been prescribed glasses only 60·9% had their glasses with them when they attended their medical examination.

The proportion and number of children who had been prescribed spectacles in each of the 10 visual impairment categories is shown in Table 3. The most striking feature of this table is the number of children with perfect vision who had spectacles. Although the proportion with spectacles in this group was small (2–3%), it represented between 200 and 300 pairs of glasses. Nearly one-third of children with minimal bilateral distant defects had a pair of spectacles, as did one-fifth of those with a vision defect in one eye only. The latter constituted a large group of children, 80% of whom had a defect of 6/9; in most of the remainder the defect was 6/12.[5]

Children who had a near vision defect with perfect distant vision were less likely to have been prescribed spectacles than were children with isolated distant vision defects. Approximately half of the children with near and far defects in only one eye had been prescribed spectacles, as had all but eight of those with marked impairments of both near and distant vision in both eyes.

The prevalence of spectacle prescribing according to sex, social class, and region of residence is presented in Table 4. The value tabulated is the proportion of children said by either parent or the examining doctor to have spectacles (definite and possible spectacle groups combined). Conclusions which could be drawn from a table showing the proportion of children who definitely had spectacles were exactly the same, and therefore only one set of values is tabulated here.

More girls (12·6%) than boys (10·8%) had spectacles ($p<0 \cdot 01$). The difference for both social class and region do not reach statistical significance.

The prevalence of visual defects is shown in Table 4 alongside the prevalence of spectacles prescriptions. It is clear that the excess of spectacles in girls is exactly what we should expect from the excess of defects. Similarly the slight variation in prevalence of spectacles by social class closely mirrors variation in the prevalence of defects. That there is close correlation between these two values is illustrated by calculating the ratio of 'spectacle prevalence' to 'defect prevalence.' This ratio remains remarkably constant in the two sexes and across the different social classes. The number of spectacle prescriptions is approximately half the number of children with visual defects in all groups.

Although the difference in prevalence of spectacle prescriptions across the regions is not statistically significant, it can be seen from Table 3 that the prevalence does not vary in the same way as defect prevalence. This is illustrated by the fluctuating spectacle-defect ratio. The fluctuation suggests that, after allowance is made for variation in the

Table 3 *Proportion of children prescribed spectacles in different visual acuity categories (n=12 840)*

Category of defect	Definite spectacles		Possible spectacles		Total	
	%	No	%	No	%	No.
0 Perfect vision	2·1	206	1·0	96	3·0	302
1 Bilateral minimal distant defect	29·3	139	2·5	12	31·8	151
2 Bilateral mild distant defect	65·7	113	4·1	7	69·8	120
3 Bilateral marked distant defect	88·9	96	0·9	1	89·8	97
4 Unilateral distant defect	19·8	117	2·9	17	22·7	134
5 Bilateral near defect	16·8	32	1·6	3	18·4	35
6 Unilateral near defect	10·8	29	0·4	1	11·2	30
7 Unilateral mild mixed defect	44·7	96	5·6	12	50·2	108
8 Unilateral marked mixed defect	49·0	73	6·7	10	55·7	83
9 Bilateral mild mixed defect	59·6	328	2·0	11	61·6	339
10 Bilateral marked mixed defect	91·3	105	1·2	2	93·0	107

Table 4 *Prevalence of spectacle prescribing*

		Number of children in group	*Proportion said by parents or doctor to have been prescribed spectacles* %	*Proportion of children with less than perfect vision (6/6 6)* %	*Spectacle defect ratio (column 1/column 2)* %
Sex	Girl	6652	12·6	24·7	0·51
	Boy	7104	10·8	20·8	0·52
Social class	I	759	12·6	23·7	0·53
	II	2896	11·0	20·6	0·53
	IIIN	1111	11·5	21·8	0·53
	IIIM	5379	11·5	21·4	0·54
	IV	1496	11·5	23·6	0·49
	V	481	14·3	25·7	0·56
Standard region	Scotland	1369	10·7	23·3	0·46
	North	860	10·9	20·1	0·54
	York and Humberside	1375	11·8	21·7	0·54
	North-west	1703	11·3	22·2	0·51
	East Midlands	906	11·1	25·0	0·44
	West Midlands	1444	12·5	19·9	0·63
	Wales	799	12·4	22·8	0·54
	East Anglia	485	11·5	22·5	0·51
	South-east	3763	12·4	21·7	0·57
	South-west	1018	10·4	22·6	0·46

prevalence of defects, children are less likely to be prescribed spectacles in Scotland and the South-west and more likely to be prescribed them in the West Midlands.

Disagreement between parents and doctors about whether the child had spectacles was more common among children with perfect vision (Table 5). This group and those with only a minor defect were less likely to have brought their prescribed spectacles to the medical examination. Children in the lower social classes were also less likely to be carrying their spectacles with them when they were seen by the doctor (Table 6). Indeed a trend in this phenomenon could be observed across the different classes; 69·8% of those in class I and 47·8% of those in class V brought their spectacles with them. In contrast spectacle usage did not appear to be influenced by sex or region of residence.

Tables 7, 8, and 9 present data relating headache to spectacle prescribing. Spectacles were prescribed more frequently to children whose mothers reported that they experienced headaches (more often than once a month); 15·4% compared with 11·2%. The prevalence of defects was also slightly raised among this group, but spectacle prescribing remained increased even when this was taken into account.

Headaches were more common among the group of children who failed to bring their spectacles to the medical examination and among the 'possible spectacle' group. They were also common among children who had spectacles but had no visual defect. These findings fit the hypothesis that children with

Table 5 *Use of spectacles by severity of vision defect (n=12 840)*

Category of defect		*Number of children who may have been prescribed spectacles*	*% of those in column 1 who brought their spectacles to the medical examination*	*% of those in column 1 who did not bring their spectacles to medical examination*	
				Parents and doctor agree that child has spectacles	*Either parent or doctor but not both say child has spectacles*
0	Perfect vision	302	36·8	31·5	31·8
1,4	Minor defects	285	60·0	29·8	10·2
2,3,5, 6–10	Other defects	919	73·4	21·4	5·1

χ^2_4 $p<0·0001$

Table 6 *Provision and use of spectacles: social class, region, sex (n=12 840)*

	Number of children who may have been prescribed spectacles	*% of those in column 1 who brought their spectacles to the medical examination*	*% of those in column 1 who did not bring their spectacles to medical*	
			Parents and doctor agree that child has spectacles	*Either parent or doctor but not both say child has spectacles*
Social class (n=12 122)				
I	96	69·8	19·8	10·4
II	320	70·1	19·4	10·5
IIIN	128	65·6	14·8	19·5
IIIM	618	60·2	23·9	15·9
IV	172	57·6	29·1	13·4
V	69	47·8	42·0	10·1
χ^2 p<0·01				
Standard Region (n=13 722)				
Scotland	146	68·5	21·9	9·6
North York & Humberside	94	60·6	25·5	13·8
North West	162	60·5	26·5	13·0
East Midlands	193	60·6	22·3	17·1
West Midlands	101	59·4	24·8	15·8
Wales	181	57·5	26·0	16·6
East Anglia	99	59·6	29·3	11·1
South East	56	67·9	16·1	16·1
South West	466	62·6	22·2	15·2
	106	59·4	17·9	22·6
χ^2 p=NS				
Sex (n=13 756)				
Boys	770	60·0	24·4	15·6
Girls	840	61·7	23·8	14·5
χ^2 p=NS				

perfect vision and those with minor visual defects are more likely to be prescribed spectacles if they also complain of headaches.

Discussion

Between 10% and 12% of the 10-year-old children in this cohort had been prescribed spectacles. But one in five of the children with spectacles had normal visual acuity, and between 15% and 10% had only minimal defects. Over a third of children who had spectacles came to their medical examination without them, which might suggest that many children who had been prescribed spectacles rarely wore them. Thus the overprescribing of spectacles identified among the 16-year-olds of the 1958 cohort is apparently occurring among younger children also.

Table 7 *Prevalence of spectacle prescribing among children who experience headaches more often than once a month (n=12 316)*

	% with spectacles	*% with visual defects*	*Ratio of spectacles to defect*
Children with headaches	15·4	24·3	0·63
Other children	11·2	21·7	0·53
Statistical significance	p<0·001	p<0·05	

The suggestion has been raised[6 7] that unnecessary spectacles can cause a deterioration in visual function. This hypothesis has not been rigorously tested and a more substantive criticism of overprescribing can be made on the grounds of wastage of scarce resources. The price of a single pair of spectacles is not great. The average cost to the National Health Service for a prescription, including lenses, frames, and optician's professional fee, is £15·00 (1984 prices). However, if we accept that 35% of prescriptions to 10-year-olds are unnecessary, and we assume that this level of overprescribing is equally common at all ages in school children, we can calculate that at any one point in time the sum which has been spent on spectacles which are unlikely to benefit children

Table 8 *Provision and use of spectacles. headaches (N=13 109)*

	Number of children	*Proportion of children experiencing headaches at least once a month*	
		%	*No.*
No spectacles	11 574	10·7	1237
Spectacles available for medical examination	954	12·9	123
Spectacles not brought to medical examination			
Definite spectacles	364	17·0	62
Possible spectacles	217	18·4	40

χ^2_3=p<0·001.

Table 9 *Proportion of children experiencing a headache at least once a month (n=12 316)*

	Children with spectacles		*Children without spectacles*		*Statistical significance*
	%	*No.*	%	*No.*	
Visual defect present	13·4	140	11·4	185	NS
No defect	18·2	36	10·6	997	p<0·001

is about £5·4 million (nearly £30,000 per health district).

Were these spectacle prescriptions really necessary? The principal weakness of this study lies in the measurement of visual acuity. VA charts used as they have been in this study by a series of medical officers with variable training in a multitude of schools and clinics constitute a very blunt instrument for measuring visual function.

Thus it is likely that a proportion of the children who appeared to have perfect visual acuity but who nevertheless had been prescribed spectacles were inadequately tested. Some of them may have had a lower visual acuity than that recorded, but it is unlikely that the acuity was seriously impaired. Others may have had mild degrees of astigmatism or hypermetropia, which may be present without a defect of acuity. Some of the latter children may have been prescribed spectacles to treat latent or overt squint. 18% of the group of children with apparently perfect visual acuity and spectacles were reported to have a squint or to have had one in the past.

Children with 6/9 vision constitute another large proportion of all children with spectacles; and if, as suggested above, some of the group with perfect acuity actually had a minor defect which had not been detected, the true proportion could be even larger. However, evidence that children with 6/9 vision benefit from spectacles is anecdotal. It could be argued that 6/9 vision is due to normal variation in the refractive power of the 10-year-old child's eye. Correcting refraction with spectacles to the arbitrary level of 6/6 imposed by the Snellen chart may be inappropriate. However, many of those working in the children's eye clinics do treat these defects because they believe that minor degrees of visual impairment can interfere with learning. There is little evidence to support this idea, and a recent study[4] has presented evidence which suggests that minor visual impairment does not interfere with learning.

There is no reason why the value of spectacles should not be tested in randomised controlled clinical trials. Such trials should be able to establish which type of children with which type of impairment benefit from spectacles and in what way. Although lack of interest on the part of the ophthalmologists managing children's eye clinics, attitudes and beliefs among parents, and financial interests among those who prescribe spectacles may present as obstacles to such trials, none of these should prove insurmountable.

Trials of treatment will not be conducted overnight, and it will be some time before definitive answers are available. However, this study would suggest that there is considerable room for rationalisation of prescribing in the meanwhile. For example regional variation in spectacle prescribing could be examined. There may be good reasons why such variation exists, but equally the differences may simply be a matter of habit. Further information on geographical variation should be available from family practitioner committees, which handle fees for all spectacles prescribed to children in many parts of the country.

Follow-up visits by children who have been prescribed spectacles might lead to a greater awareness of which children benefit. Such visits could be used to assess whether symptoms such as headaches or poor academic progression improve after spectacles are prescribed. Questions could be asked to assess the extent to which spectacles are actually worn. Simple self-auditing procedures such as these might on their own lead to a reduction in prescribing or at least to a halt of the current tendency to prescribe spectacles to children with milder and milder visual defects.

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Trabeculectomy with iridencleisis

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SUMMARY An iridencleisis is added to the original trabeculectomy technique of Cairns as modified by Watson for the surgical treatment of glaucoma. The steps are described with special reference to the fashioning of the iridencleisis as an iris tongue lying curled upon itself with the pigmented layer lining the inner aspect of the iris resting between the scleral flaps. Two series of patients from Africa and one series from the USA show postoperative intraocular tensions of 24 mmHg or less in 90% to 98% of patients. The Caucasian series from the USA had 94% with pressures of 21 mmHg or less. At least 90% in all three series were controlled *without* continued glaucoma medication.

Trabeculectomy has gained acceptance for glaucoma surgery. The original technique as described by Cairns[1] and modified by Watson[2] included a peripheral iridectomy. Twenty years earlier Stallard[3] had described a full-thickness filtering procedure which incorporated an iridencleisis. Forty years ago, in 1944, Iliff[4] summarised: Iridencleisis is superior to trephining as an initial operative procedure and the complications are less severe. He was saying this in relation to the surgical control of glaucoma in the Negro.

After performing 35 trabeculectomies with peripheral iridectomies on black patients in Sierra Leone, West Africa, 1972–3, one of the authors (LG) realised that under 50% achieved intraocular pressures of 24 mmHg or less. This was comparable to the experience of Welsh[5] in Durban, South Africa. It became evident that trabeculectomy surgery of black patients resulted in only a fair success rate at that time. It was not until 1977 that David, Freedman, and Luntz[6] reported a 73% control of intraocular pressure by the Cairns and Watson techniques, and a 91·6% control following reoperation, with or without additional medications.

What we realised in 1973 in West Africa was that, by making an iridencleisis a part of the trabeculectomy procedure, a success rate of up to 90% *without* additional medication could be achieved. Special care was exercised *not* to manipulate the iris tongue, so that it lay curled upon itself with the pigmented layer lining the inner aspect of the iris resting between the scleral flaps.

Materials and methods

This study includes three series of patients.

Series A represents 100 consecutive black patients receiving a trabeculectomy with iridencleisis in 1982 with an average range of follow-up of one year, as performed by I Gralle at the Lunsar Eye Hospital, Lunsar, Sierra Leone, West Africa. Skin snips for onchocerciasis were positive in 48%. 19% showed severe findings associated with onchocerciasis (keratitis, microfilaria in anterior chamber, posterior synechiae, iritis, chorioretinal lesions, and optic atrophy). An operating microscope was used.

Series B represents 100 black patients with glaucoma *not* associated with onchocerciasis, with an average range of follow-up of four years. Surgery was done by E Koeth at the Lunsar Eye Hospital, Lunsar, Sierra Leone, West Africa, during 1977-82. Operating loupes were used.

Series C represents 50 consecutive cases of Caucasian patients operated on by L Gess at Alexandria, Minnesota, USA, during 1975–82, with an average range of follow-up of five years. An operating microscope was used.

The findings recorded included age, sex, visual acuity, and preoperative intraocular tensions. The 'ultimate' postoperative tensions are noted along with the average time in years of follow-up. The condition of blebs, the number of patients needing additional glaucoma medication, and the complications are listed under 'Results'.

TECHNIQUE

The steps in the procedure of trabeculectomy with iridencleisis are as follows (Figs 1 and 2).

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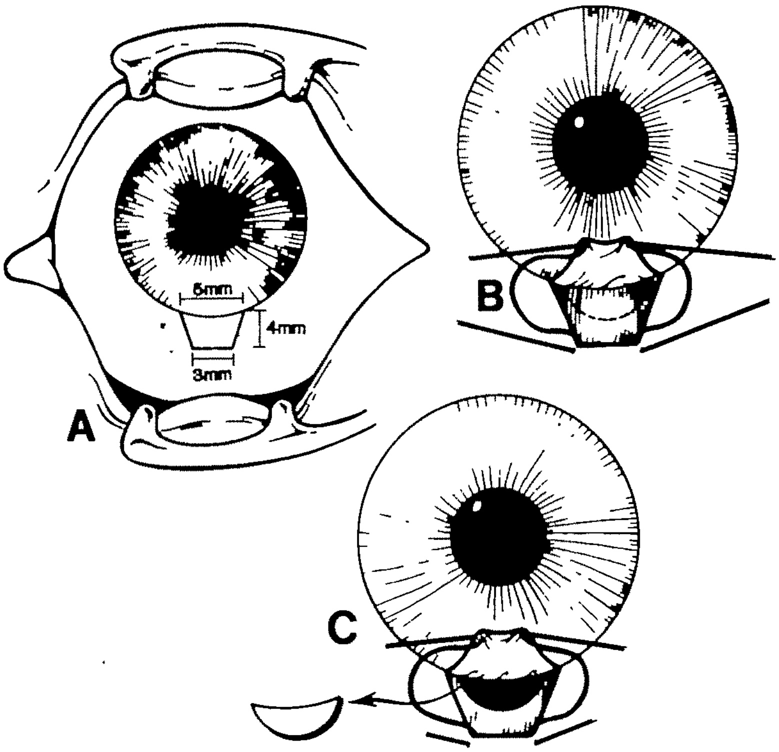

Fig. 1

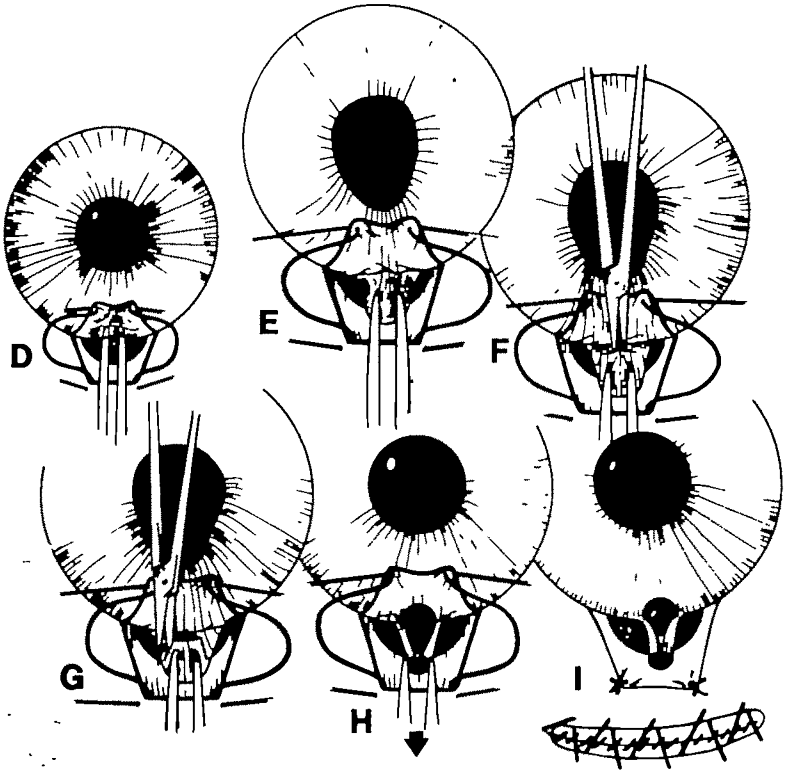

Fig. 2

A (Fig. 1). Following a limbal based conjunctival and tenon's capsule flap a razor blade scratch incision less than half the scleral thickness outlines a flap with the base 5 mm, the sides 4 mm, and the top 3 mm.[7]

B. The scleral dissection extends into clear cornea anteriorly. The apex extends one-half the distance of the flap dissection, going beyond the scleral spur.

C. The trabecular block of tissue is dissected off from the scleral spur.

D, E (Fig. 2) A Max Fine curved forceps without teeth reaches into the anterior chamber to grasp the iris just above its mid portion. If the iris is bulging, it can be grasped outside the anterior chamber and the iridencleisis fashioned. If the bulging is confusing, a small iridotomy will deflate it, and the iris can be grasped from within the anterior chamber in its normal position.

F. A circumferential incision is made in front of the Max Fine forceps with pointed iris scissors.

G. One blade of the scissors is placed inside the circumferential opening and radial cuts are made on each side.

H. The tongue of iris tissue is laid down on the deep scleral bed. The tip of iris should extend beyond the trabecular dissection. It is not manipulated, so that it naturally curls up on itself with the pigment layer lining the inside.

I. The preplaced 7–0 absorbable sutures are drawn up to bring the superficial scleral flap back into position. Additional sutures are placed if there is gaping of the wound edges. Tenon's capsule and conjunctiva are closed separately with the 7–0 absorbable running suture.

Results

The results are shown in Tables 1–5.

Of the patients receiving surgery for glaucoma in Africa 70% were male, while nearly 70% of the Caucasian patients in the USA were female. Preoperative tensions were higher in the African population. Visual acuities were unchanged or improved in

Table 1 *Age and sex (in percentages)*

	Series A	*Series B*	*Series C*
Age			
<10	3	0	2
11–20	8	4	0
21–30	9	5	4
31–40	21	19	8
41–50	20	24	19
51–60	21	25	26
>61	18	23	46
Sex			
Male	78	71	34
Female	22	29	66

Table 2 *Preoperative intraocular pressures*

Pre op intraoperative pressures, mmHg	*Series A*	*Series B*	*Series C*
15–21			4
22–24			18
25–30	4	5	26
31–40	31	29	26
41–50	43	38	26
51–60	16	21	
61–80	6	7	

The patients in series C with pressure readings under 25 mmHg had significant glaucomatous nerve head and field changes.

Table 3 *Visual acuity changes (in percentages)*

	Series A	*Series B*	*Series C*
Unchanged	51	39	24
Improved (by at least one line)	20	31	52
Decreased (by at least one line)	29	30	24

Table 4 *Postoperative results (in percentages)*

	Series A	*Series B*	*Series C*
Range of postop. follow-up	½ to 1½ years	2–7 years	2–9 years
Average	1	4	5
Last intraocular pressures (mmHg)			
0–5	2	5	2
6–10	5	19	22
11–15	21	31	32
16–21	50	33	38
22–24	13	9	4
25–30	7	3	2
31–40	2		
>40	1		
Blebs: diffuse			72
Cystic	Not recorded	Not recorded	20
Absent			8
Controlled patients requiring continued glaucoma medication	10	8	8

Table 5 *Complications (in percentages)*

	Series A	*Series B*	*Series C*
Hyphaemas	6	3	24
Prolonged anterior chamber shallowing	2	4	4
Malignant glaucoma	2	0	0
Repair of wound	0	1	2
Reoperation	4	0	0
Iritis	Not recorded	Not recorded	2
Vitreous loss	0	0	0
Cataract formation	Not recorded	Not recorded	8

at least 70% of each series. 90% to 98% achieved an intraocular pressure (IOP) of 24 mmHg or less. 94% of the Caucasians in series C had an IOP of 21 mmHg or less. At least 90% in all three series were controlled without continued glaucoma medication. One half of those requiring further medication in series C were diabetics.

The most frequent complication was hyphaema. The greatest measured 2·5 mm high. All cleared within two weeks, usually in two to four days. Prolonged anterior chamber shallowing occurred in 2% to 4% in each series.

Discussion

It is interesting to note that over 70% of the patients receiving surgery for glaucoma in Africa were male, while nearly 70% of the Caucasian patients in the USA were female.

Visual acuities were unchanged or improved in at lest 70% of each series. 90% to 98% achieved intraocular tensions of 24 mmHg or less; in 94% of the Caucasians in series C it was 21 mmHg or less. At least 90% in all three series were controlled without continued glaucoma medication. One-half of those requiring further glaucoma medication in series C were diabetics.

A diffuse or cystic bleb was usually present in the patients who had a successful result. R Witmer (personal communication) notes that 2–3% are successful without a bleb. He suggests that the filtration may go through Schlemm's canal in those cases, so he prefers to include the trabecular meshwork in his block of dissection.

J E Cairns of Great Britain (personal communication) has also expressed concern about hyphaemas, iritis, and sympathetic ophthalmia. The patients in series C had 12 small hyphaemas. The greatest measured 2·5 mm high. All cleared within two weeks, usually in two to four days. There were no late hyphaemas.[8] There were no cases of iritis that did not respond to cycloplegics of the atropine strength. Often movement of the pupil was achieved with homatropine or tropicamide. Hyoscine was used on several occasions. Topical steroids were used. Rarely subconjunctival or systemic steroids were necessary.

Sympathetic ophthalmia was not encountered in the more than 1000 procedures performed in Sierra Leone, West Africa (E Koeth, I Gralle, J Stilma, H Friesen, M Scudder, E Ceesay, T Gess, L Gess), in Pakistan (N Christie), or in the USA (T Gess, L Gess).

Some authors[9,10] consider that filtering procedures pose special difficulties in the Negro race. Krishna M Moni[11] observed that intraocular pressures of 28 mmHg or less were achieved in 85% of the African eyes treated with trabeculectomy and the standard peripheral iridectomy. African patients in series A and B in this study of trabeculectomy with iridencleisis had an intraocular pressure of 24 mmHg or less in 90% or more of the cases.

Other authors[4,12-15] report results that are similar between blacks and Caucasians. Our findings in the three different series from two continents show similar results in spite of the surgery being done by three different surgeons. Each surgeon, however, fashioned the iridencleisis in the same manner. There were no segmental iridectomies, as was done in the original procedures using iridencleises. Also the original iridencleises had the iris lying flat rather than being allowed to roll up into a tube with the pigmented layer lining the inside. Occasionally excision of Tenon's capsule was done when reoperation was necessary, especially in patients under 40 years of age.

Series A, which included patients with onchocerciasis, surprisingly did not have significantly more complications than the other two series. However, the chart records do not specifically record the number of patients with iritis or uveitis, which most likely would have been increased by the nature of the onchocerciasis infestation. Sandford-Smith[16] noted that nearly one-half of the cases that failed in his series had positive skin snips. Kietzman[16] also observed only 50% control in onchocercal eyes undergoing trabeculectomy.

It is a general consensus that trabeculectomy has a harmful effect on the lens, leading to sclerosis.[17] Of the four patients in series C with development or progression of postoperative cataract two have had extracapsular cataract interactions with posterior chamber lens implantations through corneal incisions. Visual acuities are 20/20 and 20/25. Intraocular pressures are 18 and 19 mmHg.

In spite of apparent cataractogenic effects, troubling hyphaemas, which readily and spontaneously absorb, and rare prolonged flattened chambers, Lowenthal[18] considers that a surgical approach to open-angle glaucoma is the procedure of choice. Argon laser therapy, while being effective in controlling the intraocular tension[19] in 77% of cases, still has 82% of patients receiving glaucoma medication.[20] In this series of trabeculectomies with iridencleises 90% received no medication postoperatively. It remains to be seen if patients treated with argon laser will have rising intraocular tension in the succeeding years that ultimately requires a filtering operation.

The present study records encouraging statistics for iridencleisis in trabeculectomy for partial-thickness glaucoma filtration. In black patients with glaucoma it was found to be especially effective in reducing intraocular pressures to normal. Onchocerciasis patients with synechiae responded well. The procedure was effective for Caucasian glaucomatous patients, with 92% needing no further glaucoma medication.

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Argon laser trabeculoplasty in exfoliation syndrome

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SUMMARY A retrospective study of the effects of argon laser trabeculoplasty on a consecutive series of 44 phakic patients (55 eyes) with exfoliation syndrome glaucoma is reported. The follow-up was 12 to 23 months, mean 15 months. At an individual level laser trabeculoplasty was successful in 70% of the patients and 40% were able to reduce or stop their medication. Two patients showed 'late failure' at 15 months after initial control. An early rise of intraocular pressure was fairly common in the exfoliation group, and perhaps these patients need particularly careful monitoring during the initial hours following argon laser trabeculoplasty. A beneficial effect was noted on diurnal curve fluctuations and peak intraocular pressures.

Several investigators have shown that argon laser trabeculoplasty (ALT) is an effective method of treatment in many patients with exfoliation syndrome glaucoma.[1-3] It has been noted that the prognosis of exfoliation glaucoma patients treated either medically and/or surgically is poorer than that of simplex glaucoma patients.[4,5]

This study retrospectively considers the results of ALT performed in 1982 at the University Hospital, Uppsala, on phakic patients with exfoliation syndrome glaucoma.

Materials and methods

A consecutive series of 44 phakic patients (55 eyes) with exfoliation syndrome were studied who received argon laser trabeculoplasty between January and December 1982. This allowed for a 12- to 24-month follow-up for each patient. Four cases with previous filtering surgery to the eye concerned were excluded.

Prior to laser treatment the patients were admitted to hospital and a diurnal pressure curve consisting of seven readings, performed with a Goldmann applanation tonometer, was plotted. Laser trabeculoplasty was performed by a coherent system argon laser, Lasertek 40A, to 180° of the trabecular meshwork at a sitting (except two patients who received 90° laser therapy per session), with the number of burns varying from 23 to 60 (mean 40) to each half of the angle meshwork. A 50 μm spot size and 0·1 second time exposure was used (except one case where 0·2 second was employed), and the power was adjusted to obtain a suitable end point for the individual. Seven different surgeons carried out the laser treatment of these patients.

After laser treatment the intraocular pressures were measured on the patients in hospital to detect any early pressure rise, and some patients were started on corticosteroid drops.

Subsequent pressure measurements were taken at various intervals, with the patient either in hospital, in which case a diurnal curve of seven readings were plotted, or as an outpatient, when either a single set of readings or three readings spread over a morning and afternoon were recorded. Only 11 eyes had diurnal curves plotted for more than six months after the laser therapy.

It was decided that the criteria used to judge 'success' of laser treatment in a given case would be two-fold, namely (1) an average fall in mean intraocular pressure of at least 20% from the baseline value; (2) in addition, no two consecutive intraocular pressures above 21 mmHg.

Two patients who by these criteria would be judged successful cases were excluded when classification into success or failure was considered, because their medication was increased between one and nine months after laser treatment. In one case of uniocular exfoliative glaucoma the acetazolamide was increased from 125 mg tds to 500 mg bd 9 months after ALT. At that time the intraocular pressure in each eye was 11 mmHg. In the other case guttae epinephrine (adrenaline) 1% was added to both eyes despite the intraocular pressure in the lasered eye

Correspondence to Mr M B Sherwood, FRCS

having fallen from a baseline mean of 23 to 17 mmHg at six weeks after laser treatment. The intraocular pressure estimations following the increase in medication were also not included in the study. One patient who by our criteria would be classified as a failure and who received an addition of acetazolamide 375 mg a day to his medical therapy was retained in the study because the increased medication was given secondary to poor control, and it was considered that this lack of control of intraocular pressure could not be discounted without biasing the study.

Results

Fifty-five eyes of 44 patients had laser trabeculoplasty in 1982; the mean age of the group was 70·0. Twenty-one of 55 eyes (38%) received only 180° of argon laser trabeculoplasty rather than 360° in two sessions separated by a few weeks.

Table 1 shows the effect of ALT on the mean intraocular pressure, the peak intraocular pressure, and the pressure irregularity of the diurnal curve. This last was given by the standard deviation of the seven pressure readings from the mean measured over the 24-hour period. A composite reading for each patient consisting of all pressure recordings from one to six months after ALT and also a composite of the 9, 12, and 15 month readings are shown in the table, but the individual timed results are seen in Figs. 1 and 2. A one-tailed paired *t* test was performed, and the decrease in the mean IOP, the peak IOP, and pressure irregularity of the diurnal curve were all found to be significant ($p<0·0005$).

Table 2 shows that 70% of patients could be classified as a success according to the above criteria, but of the subgroup with a baseline mean IOP of 21 mmHg or below only 30% qualified. A second method of classification for success, as defined by the *peak* intraocular pressure being 21 mmHg or less following ALT, was considered which may be particularly appropriate for these patients with low pretreatment intraocular pressures.

In Table 3 the reduction in medical therapy following the laser treatment is shown. The total number of different medications taken (pilocarpine, adrenaline,

Table 1 *Intraocular pressure and diurnal curve changes following laser treatment*

	Baseline	*Composite 1–6 months*	*Change from baseline*	*Composite 9–15 months (52 eyes)* †	*Change from baseline*
Mean IOP mmHg (55 eyes)	25·2	17·9	7·3 (29%)	18·3	6·9 (27%)
Peak IOP mmHg (52 eyes)*	30·1	21·7	8·4 (28%)	—	
Pressure irregularity of diurnal curve (52 eyes)*	3·99	2·62	1·37 (35%)		

*Three patients did not have repeat diurnal curves from 1 to 6 months after laser treatment and are not included The average peak IOP for these three patients was 33 mmHg and fell to 28 mmHg (15%) by two weeks after ALT

†Three patients had trabeculectomy before nine months after laser treatment

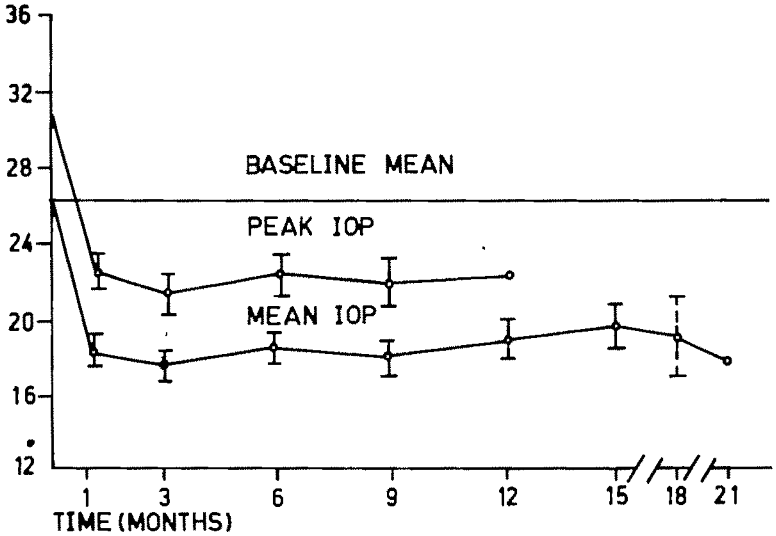

Fig 1 *Change in mean IOP and peak IOP with time Bars show standard errors.*

Table 2 *Success rates following laser treatment*

	Criteria for success of 20% + fall in IOP and IOP 21 mmHg or less	*Criteria for success of peak IOP <21 mm Hg for 1–6 months*
Total group	37/53* (70%)	30/52*† (58%)
Baseline mean IOP with medical treatment >21 mmHg	34/43 (79%)	24/42† (57%)
Baseline mean IOP with medical treatment <21 mmHg	3/10 (30%)	6/10 (60%)

*Two patients classified as 'successful' but who had an increase in their medication not included (see 'Methods')
†One patient without diurnal curve measurements beyond two weeks after laser treatment not included.

Table 3 *Reduction in medical treatment*

Mean initial number of medications	2·00
Mean final number of medications	1·58
Number of patients off all medication	8/55 (15%)
Number with reduced number of medications	14/55 (25%)

timolol, and carbonic anhydrase inhibitors) was used to assess this, and the few cases of small alterations in strength and dosage of a particular agent were ignored. 15% of patients were able to stop all antiglaucoma medical treatment and a further 25% to reduce the number of their medications. These results are demonstrated graphically in Fig. 3.

Table 4 shows the early spike in intraocular pressure that can occur in the 24 hours following ALT. The best parameter to consider is perhaps a comparison with the diurnal curve peak intraocular pressure in the 24 hours before laser treatment, and it is of note that there were six cases (7%) with an increase of 10 mmHg or greater. Many previous authors have used the immediate pretreatment reading as a baseline or the starting mean and thus an increase of pressure above the diurnal curve mean has also been shown. In this case 32 eyes (37% of laser treatments) had a pressure spike of 5 mmHg or greater, of which 14 (16%) were 10 mmHg or more above baseline.

Table 5 shows that the total quantity of laser energy applied had little effect on success rate and also compares the results of those patients who received only 180° ALT with the remainder. The mean interval between laser treatments was three weeks.

As far as the failure cases are concerned, three proceeded to trabeculectomy three to six months after laser treatment. Another patient showed a poor response for 10 months after the first 180° ALT at which stage treatment of the remaining half of the trabecular meshwork was performed. This patient subsequently did well for the next eight months.

Two of the cases were a success for a year at least, but then control was lost at 15 months and they could be classified as 'late failures.'

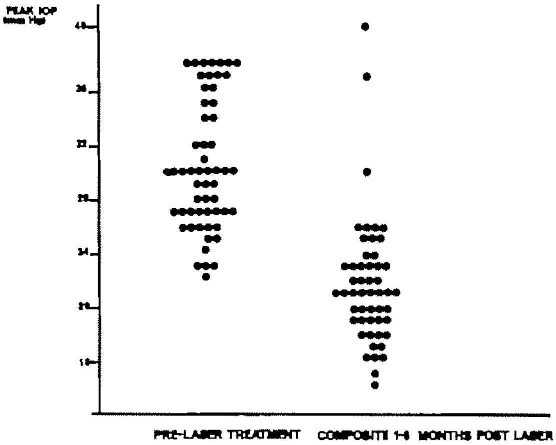

Fig. 2 *Comparison of individual peak IOPs before and after ALT.*

Discussion

In our treated group of 55 eyes (44 patients) with exfoliation syndrome glaucoma a fall in mean intraocular pressure at one year of 6·9 mmHg (27%) was recorded following ALT, the figure being derived from a composite average for each patient, of nine-month, 12-month, and 15-month readings. This fall

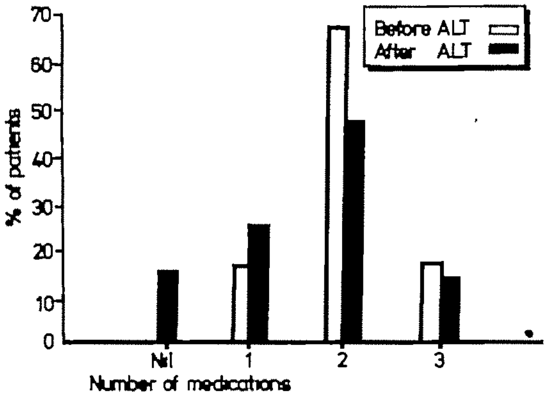

Fig 3 *Reduction in medication*

Table 4 *Early rise in peak IOP (first 24 hours)*

	Above baseline peak		*Above baseline mean*	
	1st Laser	*2nd Laser*	*1st Laser*	*2nd Laser*
Number of eyes with early elevation of peak IOP>5 mm	5	3	11	7
Number of eyes with early elevation of peak IOP >10 mm	5	1	11	3
Total	10/55 (18%)	4/32 (13%)	22/55 (40%)	10/32 (31%)

Table 5 *Laser energy applied*

	Success	*Failure*
180° Laser only	16/20 (80%)	4/20 (20%)
180° Laser × 2	21/33 (64%)	12/33 (36%)
<3 Joules	4 (80%)	1 (20%)
3–4·5 Joules	10 (67%)	5 (33%)
4·5–6 Joules	8 (62%)	5 (38%)
6+ Joules	14 (74%)	5 (26%)

Note for one success case the power setting was not recorded.

in mean intraocular pressure was despite a reduction in medical treatment in 40% of the eyes subjected to laser treatment.

Analysis of the 24-hour diurnal curves showed a concomitant fall in peak intraocular pressure of 8·4 mmHg (28%) and a reduction in the irregularity of the pressure curve of 34% between one and six months following laser treatment. Greenidge *et al.*[6] have previously described a significant reduction in the mean peak pressure of 22% and in pressure fluctuation of 25% in diurnal curves of 25 patients with primary open angle glaucoma eight *weeks* after laser treatment. Here we see similar and if anything slightly greater improvements in the diurnal curves of exfoliation syndrome patients up to 12 months after ALT.

The average fall in mean intraocular pressure reached a maximum at three months of 8·0 mmHg and then decreased a little, so that at one year it was 6·7 mmHg and by 15 months 5·6 mmHg, though it did thereafter improve to 6·1 mmHg by 18 months (Fig. 1). It is difficult to see whether there is a loss of effect of the laser treatment with time, as of course medical therapy was reduced or stopped in 40% of the eyes. Another factor confusing the issue is that the poor results of the three cases that proceeded to trabeculectomy are not included at the later time periods, which should theoretically lead to a marginal improvement in group results later on.

It can be seen from Table 5 that the amount of laser energy applied to the trabecular meshwork had no significant effect on the percentage of success of cases. The finding of slightly improved results of 80% success for the patients receiving 180° laser compared with only 64% success for those receiving 2×180° laser is probably an artefact due to the fact that those patients who responded well did not have a second laser treatment. This impression is enhanced by the knowledge that patients receiving their second laser treatment within two weeks of the first—that is, before the effect of the first laser treatment could be fully determined—had an 80% success rate, like those receiving only 180° of laser compared with 38% for those three weeks or longer between treatments.

At an individual level, by our criteria of a fall in intraocular pressure of at least 20% and in addition no two consecutive IOPs above 21 mmHg, 70% of the treated group qualified so far as a success (mean follow-up 15 months). At one year this was even higher (74%), but two patients who initially showed well controlled intraocular pressures subsequently 'failed' at 15 months This finding of late failure among the exfoliation glaucoma patients has been documented by Pohjanpelto who described it in 10 out of his 93 initially successful exfoliation cases.[2] Wilensky and Weinreb[7] also described two cases of late failure, one of which was a patient with exfoliation glaucoma.

The 10 patients who, with their medical therapy, had starting mean intraocular pressures of 21 mmHg or less showed only a 30% success rate by our criteria compared with a 79% success rate in those patients with a baseline intraocular pressure above 21 mmHg. In six out of the seven failures of this group classification was due to lack of the required 20% fall in intraocular pressure, the mean intraocular pressures remaining below 21 mmHg. It has been previously shown that the lower the intraocular pressure before laser the smaller is the decrease that can be expected both numerically and in percentage terms.[18] It may therefore be unreasonable to apply the requirement of a 20% fall in intraocular pressure in this subgroup as a method of judging success. All 10 of these patients had elevated prelaser peak intraocular pressures (average 24·7 mmHg), and control of the peak pressure to 21 mmHg or below may be a better criterion of success for this subgroup. In these terms six (60%) could be graded 'successful.'

As mentioned above, all patients received laser therapy to only 180° of the meshwork at a time. In our study there were six cases of intraocular pressure rises of over 10 mmHg in the immediate post-treatment hours, five of the six occurring after the first 180° laser session. Indeed one patient had a rise in pressure to over 60 mmHg from a starting peak intraocular pressure of 38 mmHg and required osmotic agents to relieve symptoms. It may further be noted that none of the 22 eyes (18 patients) with phakic chronic simple glaucoma who received ALT at the same department by the same surgeons between January and December 1982 had an early IOP rise of 10 mmHg or greater.

Weinreb *et al.*[9] had only one of a mixed group of 20 patients treated with 180° ALT to the anterior meshwork who showed a pressure rise of 10 mmHg. Thomas *et al.*[3] reported three of 102 eyes treated with 2×180° ALT to the posterior meshwork, with pressure elevation of greater than 10 mmHg above baseline. Neither of these papers compared pressure rises with peak baseline pressures. If a mean baseline pressure is considered, 14 cases (16%) of a pressure spike of 10 mmHg or greater were recorded, 11 of these occurring at the time of the first laser treatment. In view of these findings it would seem reasonable to suggest that exfoliation glaucoma patients should be even more closely monitored than others in the initial hours following ALT.

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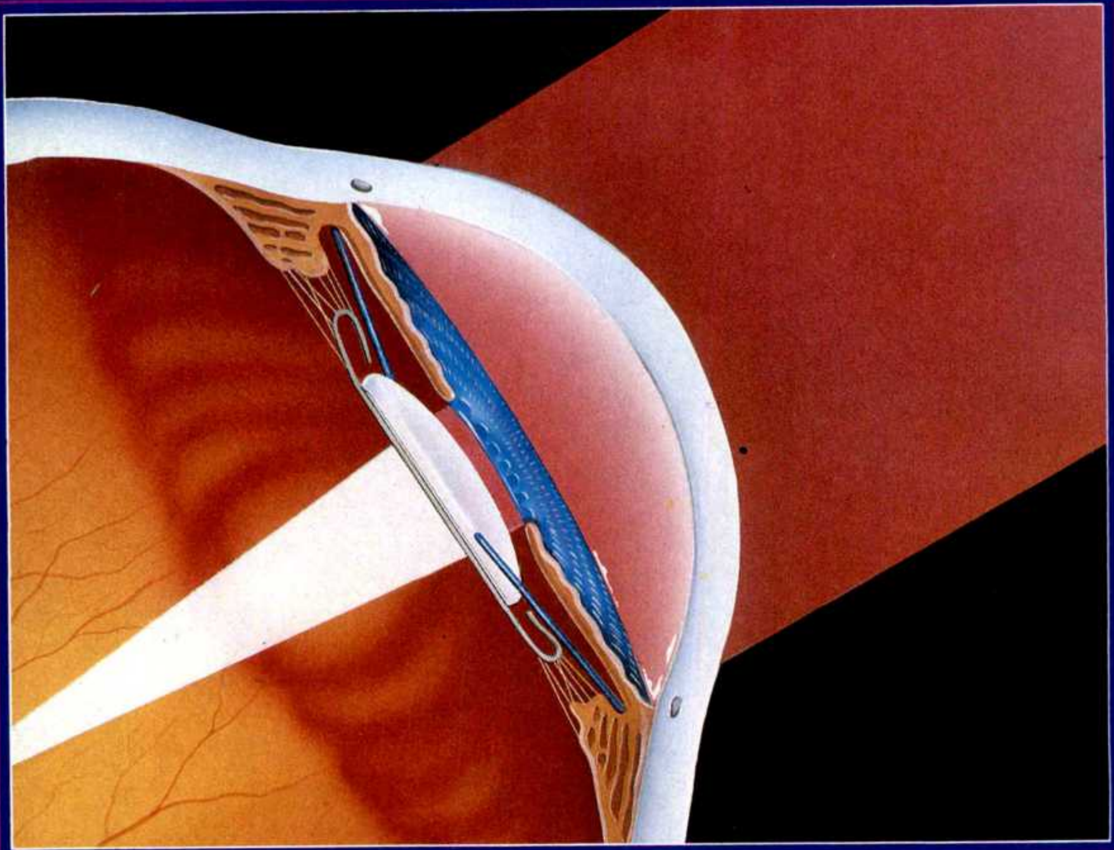

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Paralytic strabismus: the role of botulinum toxin

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From the Institute of Ophthalmology and Moorfields Eye Hospital, London

SUMMARY Five adults with acute extraocular muscle palsies followed by limited recovery of muscle function were treated with injections of botulinum toxin A to the ipsilateral antagonist of the affected muscle. Three were cases of unilateral sixth nerve palsy, one of bilateral sixth nerve palsy, and one of third nerve palsy. After a period of paralysis, during which the strabismus was overcorrected, the injected muscle recovered and binocular sensory and motor functions were restored and have been maintained for periods of up to 21 months. The treatment is a safe and effective alternative to surgery, particularly in cases in which a general anaesthetic is not advisable.

Adult neurogenic ocular palsies present problems of both diagnosis and management. Despite full neurological investigation the underlying cause may not be established,[1,2] and, even if specific treatment can be instituted, recovery of function may not be complete. Binocularity may not be restored even with a compensatory head posture, or prisms, and despite alternate patching suppression frequently develops. The timing of surgical treatment and the choice of procedure in the individual case are difficult decisions,[3] and the functional result of surgery is unpredictable, particularly after head injury or neurosurgical procedures, when fusional mechanisms may have been disrupted.[4]

In sixth nerve palsy the choice of operation depends on the extent of recovery. If the eye cannot be abducted beyond the midline, a vertical rectus muscle transposition procedure with medial rectus recession will be required.[3,5] Surgery may have to be in two stages, since the anterior ciliary arteries associated with three ipsilateral rectus muscles cannot be simultaneously operated upon in a patient over the age of 20 without risking anterior segment ischaemia.[3] When the affected eye can abduct at least 10° beyond the midline, and saccadic velocity for this is normal, a medical rectus recession and lateral rectus resection should suffice.[3,6] In either case the contralateral medial rectus may have to be recessed and adjustable or posterior fixation sutures used.[7] Surgery in third nerve palsy is less satisfactory.[8] The combination of the size of the exodeviation, the presence of a vertical deviation, and, frequently, acquired oculomotor synkinesis means that normal binocular control cannot be achieved. A satisfactory appearance in the primary position with a small field of binocular single vision will usually require operations on both eyes.[3,8]

Botulinum toxin A (BTXA) causes a flaccid paralysis of skeletal muscle by preventing the release of acetylcholine at the neuromuscular junction.[9] New junctions are formed over six to eight weeks, and the muscle gradually recovers normal activity.[10] In appropriate dosage individual extraocular muscles can be paralysed by direct injection of BTXA under local anaesthetic and the position of the eye within the orbit altered.[11,12] If binocular functions are re-established when the eyes are realigned, as the treated muscle recovers function the incomitant strabismus may not recur.[12] Five adults who would otherwise have been treated surgically for partly recovered neurogenic ocular palsies have therefore had injections of BTXA into the ipsilateral antagonist of the palsied muscle.

Patients, materials, and methods

There were three cases of unilateral sixth nerve palsy, one of bilateral sixth nerve palsy, and one of third nerve palsy (Table 1). The aetiology had been established in all cases and appropriate treatment carried out where indicated. At least six months had been allowed for spontaneous recovery to occur. The patients' general health had been assessed, particularly their suitability for general anaesthetic (Table 1). The visual acuity and visual fields were normal in all cases.

Orthoptic assessment included measurement of the angle of strabismus at near and distance fixation, and the extent of the extraocular movements (Table

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Table 1 *Description and aetiology of paralytic strabismus: five cases*

Patient	*Sex*	*Age*	*Nerve*	*Aetiology*	*General health*	*Fit for general anaesthetic*	*Interval from palsy to treatment*
1	F	19	Right VI	Infectious polyneuritis	Normal	Yes	6 Months
2	F	37	Left III	Trauma	Normal	Yes	5 Years
3	M	45	Bilateral VI	Trauma	Left hemiparesis, bulbar palsy	Yes	9 Months
4	F	73	Right VI	Hypertension	Bronchiectasis, depression	No	3 Years
5	F	18	Right VI	Pontine arteriovenous malformation	Right V and VII nerve palsies, left hemiparesis	No	8 Months

Table 2 *Pretreatment orthoptic assessment*

Patient	*Deviation prism dioptres at 6 m*	*Ocular movements*	*Saccadic velocity*	*Suppression*	*Binocular function*	
					Fusion	*Stereopsis*
1	55 Esotropia	Reduced right abduction	Normal	Intermittent	Yes	Gross
2	65 Exotropia R/L 4	Limited adduction, vertical: acquired oculomotor synkinesis	Slow adduction	Left	Yes	Nil
3	50 Esotropia	Reduced abduction bilateral	Slow abduction	Intermittent	Yes	Gross
4	30 Esotropia	Reduced abduction	Normal	Intermittent	Yes	Gross
5	45 Esotropia	Reduced right abduction	Slow abduction	Intermittent	Yes	Gross

Table 3 *Treatment schedules*

Patient	*Muscle treated*	*Subsequent treatment*	*Period of overcorrection*	*Period to stable result*
1	Right medial rectus	Nil	5 Weeks	8 Weeks
2	Left lateral rectus	Left lateral rectus at 4 weeks	3 Weeks	16 Weeks
3	Left medial rectus	Left medial rectus at 4 weeks Right medial rectus at 10 weeks	3 Weeks	14 Weeks
4	Right medial rectus	Nil	4 Weeks	6 Weeks
5	Right medial rectus	Right medial rectus at 6 weeks	3 Weeks	8 Weeks

Table 4 *Results of treatment*

Patient	*Cover test*	*Binocular function*				*Period of follow-up after stable result achieved*
		Stereopsis in seconds of arc (Titmus stereotest)	*Fusion range (degrees)*		*Area of binocular single vision*	
			Abduction	*Adduction*		
1	Esophoria	40 Seconds	4	10	Normal	21 Months
2	Exophoria	40 Seconds	4	6	30° From fixation	10 Months
3	Esophoria	40 Seconds	4	8	Normal vertical, 30° horizontal	4 Months
4	Esophoria	40 Seconds	4	10	Normal vertical, 30° horizontal	4 Months
5	Esophoria, distance esotropia Controlled by AHP	40 Seconds	2	4	Full in L gaze, 10° R gaze	4 Months

2). The saccadic velocity in the direction of the palsied muscle was judged clinically to be either normal or slow. Fusion and stereopsis were investigated on the synoptophore.

BTXA, $3{\cdot}12\times10^{-4}$ µg, was injected under electromyographic control as previously described[12] into the muscle indicated in Table 3. Clinical assessment and orthoptic measurements were repeated at one, two, and four weeks after treatment, and the injections repeated at the same dosage if necessary to produce

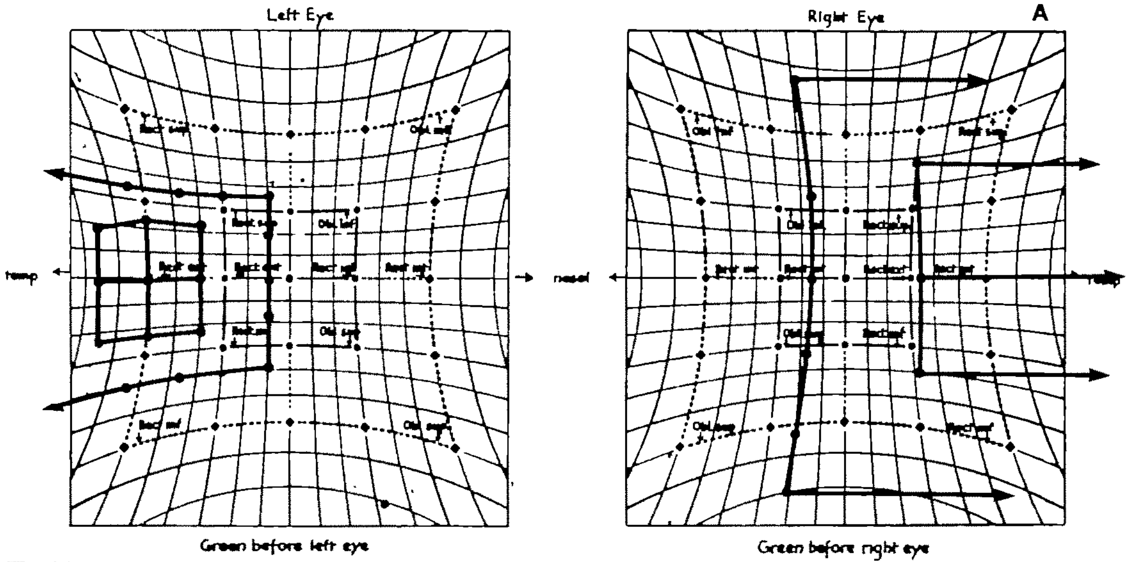

Fig. 1A

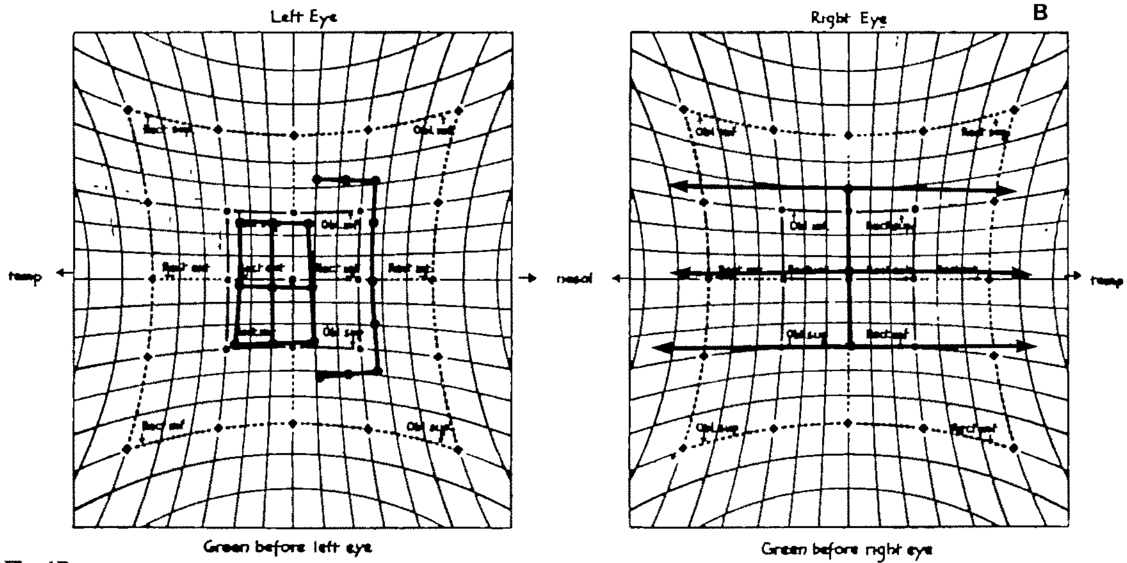

Fig 1B

Fig. 1 *Hess charts showing the effect of botulinum toxin treatment of the lateral rectus in partly recovered IIIrd nerve palsy.*

an overcorrection of the original strabismus (Table IV). In case 2 pilocarpine drops 0·1% were applied twice a day to the left eye to mediate accommodation in an attempt to re-establish fusion.[8] Follow-up thereafter has been from 4 to 21 months.

Results

There were no local or systemic side effects of the treatment.

The ocular deviation was overcorrected in all cases for a period of between three and five weeks (Table 3), when single vision could be obtained in only one position of gaze. As the treated muscle recovered function, however, the area of binocular single vision (BSV) gradually enlarged. Fig. 1A shows the Hess chart in case 2 before treatment. After the left lateral rectus had been treated, the horizontal muscles on the right eye overacted in both adduction and abduction, but there was a small central area of single

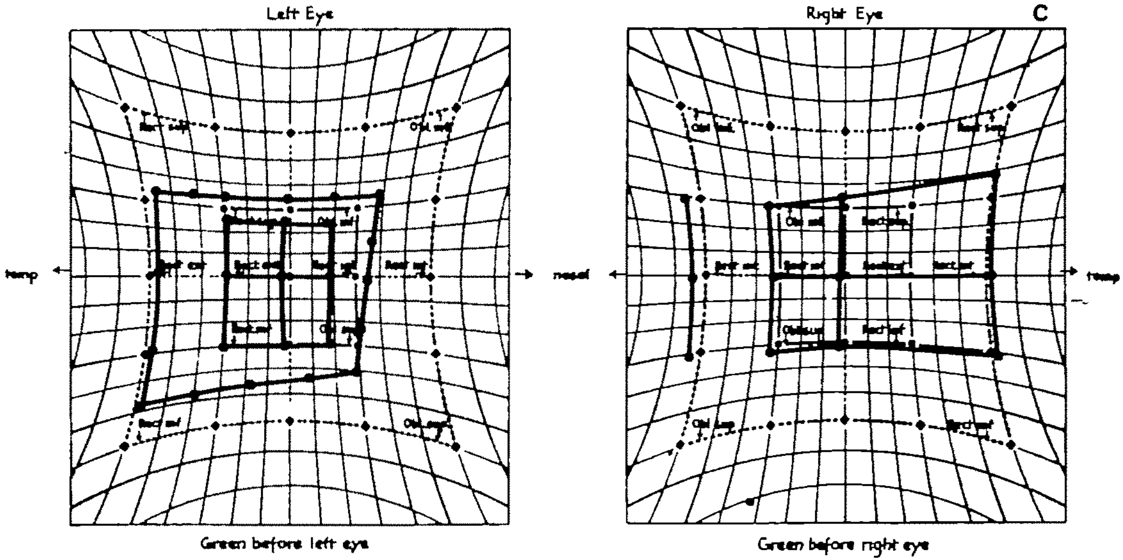

Fig. 1C

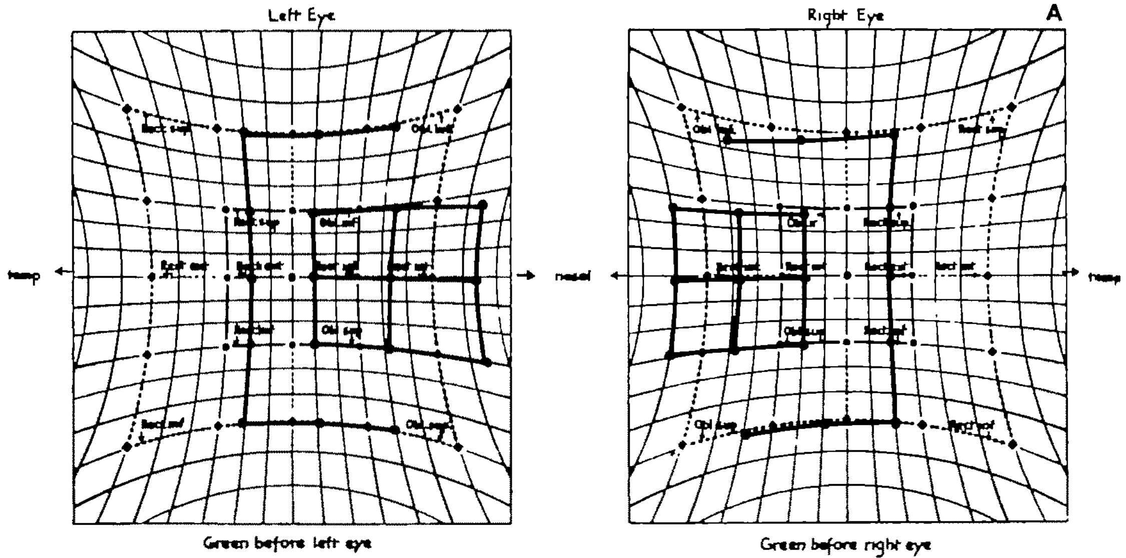

Fig. 2A

vision (Fig. 1B). The area enlarged as the lateral rectus recovered function (Fig. 1C).

Fig. 2A shows the Hess chart in case 3 before treatment. In Fig. 2B, after the left medial rectus had been treated, single vision could be obtained in left gaze, but the patient showed an increasing exotropia as he moved into right gaze. In Fig. 2C the final stable result is shown with minimal bilateral lateral rectus weakness.

Normal stereopsis and fusion were achieved in all patients after between six and 16 weeks; the field of binocular single vision was then normal in cases 1 and 4 but remained limited in cases 2, 3, and 5 because of permanent nuclear or supranuclear abnormalities of eye movement. The functional results have been maintained for periods up to 21 months (Table 4).

Discussion

Conventional treatment of these patients would

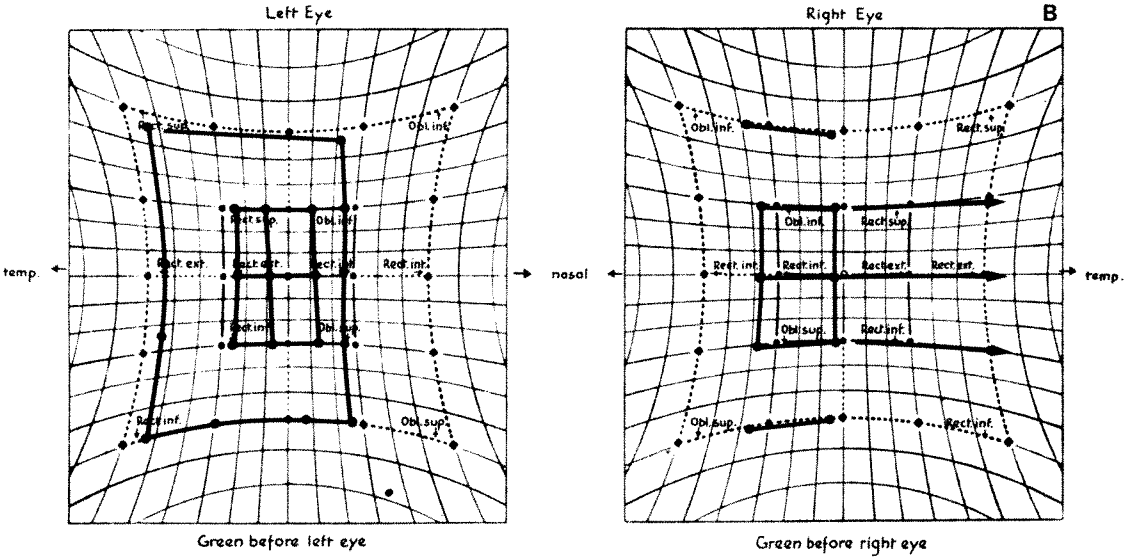

Fig. 2B

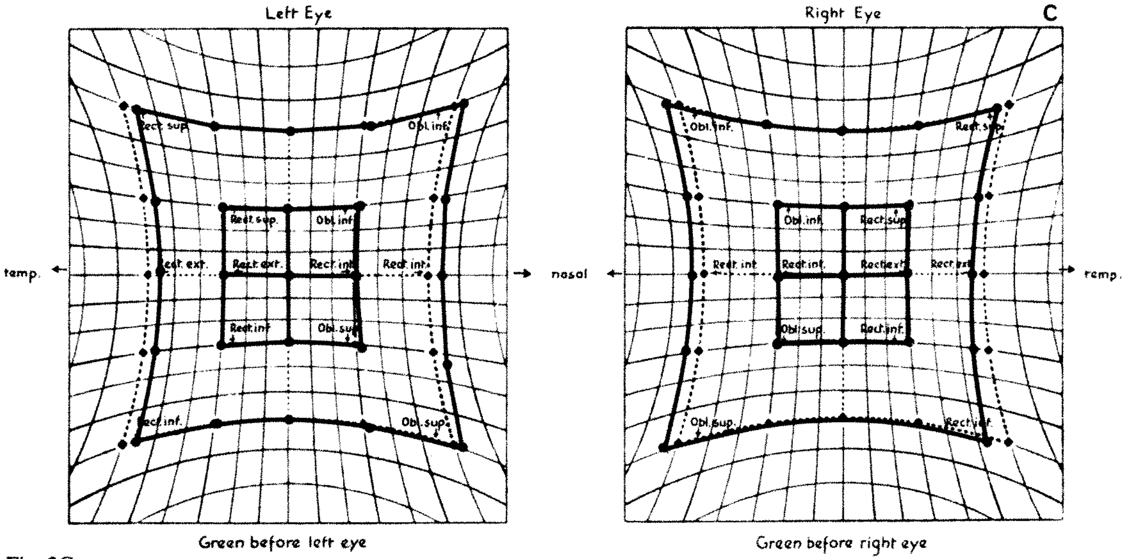

Fig. 2C

Fig. 2 *Hess charts showing the effect of botulinum toxin treatment of the left medial rectus in bilateral VIth nerve palsy.*

require surgery on both eyes for the third and bilateral sixth nerve palsies and, in two of the three cases of unilateral abduction deficit, operation under local anaesthesia. While the benefit of surgery, provided the suppression of the deviating eye was overcome, would be immediate, the potential area of binocular single vision, already limited in cases 2, 3, and 5, would be further compromised by operative reduction of ocular rotations in cases 2 and 3. The patients would be in hospital for three days and need to have local anti-inflammatory treatment for one to two weeks.

In contrast, BTXA treatment of strabismus is an outpatient procedure under local anaesthetic, and, if the muscle to be injected has not been previously operated on, the treatment is easy and painless. There are no systemic side effects,[11 12] and, while there is a theoretical danger of ocular perforation, this has not occurred in over 400 injections by the authors. The eye is padded for two hours, and thereafter no local treatment is needed.

The period of reversal of the diplopia and horizontal incomitance associated with the newly paralysed muscle was disturbing for all the patients treated. Although there was one position of gaze in which single vision could be obtained, overaction of the contralateral synergist of the injected muscle made this difficult to maintain, and the two images slipped past one another. As the paralysis recovered, the area of binocular single vision gradually increased. In case 2, after five years with suppression of the deviating image and no stereopsis demonstrable, stereo acuity of 40 seconds of arc and a near normal fusion range were achieved, and in general the quality of stereopsis and fusion regained was better than had been expected before treatment. The period of overcorrection when the deviating image is moved well away from the suppression scotoma may explain this finding.

Experience with BTXA treatment of strabismus in patients without binocular functions[12] suggests that the eye tends to drift back to the original position as the paralytic effect of the injection declines. If stereopsis and fusion had not been re-established in these cases therefore, the pretreatment status would have been restored, whereas surgery may have led to intractable diplopia.

BTXA has also been advocated in the management of acute microvascular lateral rectus palsy, when injection of the ipsilateral medial rectus, by allowing the eye to abduct passively, enables a small central area of binocular co-operation to be achieved. It is expected that the two paralysed horizontal muscles would regain function at the same rate, gradually enlarging the area of the binocular single vision. We consider that these benefits to a group of patients with a good prognosis for recovering lateral rectus function are outweighed by disadvantages. A change in neurological signs may be obscured, and the reversal of diplopia on either side of the central binocular area is likely to be very uncomfortable. We are, however, extending the use of BTXA to the treatment of the medial rectus prior to surgery in cases of persistent abduction weakness requiring vertical muscle transposition, with encouraging results.

Conclusion

BTXA treatment of partly recovered adult paralytic strabismus is a simple, safe, cheap, and effective method which avoids the risks of a general anaesthetic. A larger area of binocular single vision may be achieved than by conventional surgery.

We thank Miss C Smyth for secretarial assistance.

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Detection of optic nerve damage in ocular hypertension

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SUMMARY Thirty patients with ocular hypertension were tested for contrast sensitivity loss. Seventeen were not on treatment, and thirteen were receiving some form of pressure reducing therapy. The contrast sensitivity results of 63% of ocular hypertensive eyes were abnormal (greater than 2 SDs from the age matched norm). Thus it appears that contrast sensitivity can detect early visual loss in patients who have normal visual fields and it is suggested that this test might be used as a criterion for therapy in ocular hypertension. There was no significant difference in the intraocular pressures between patients who gave abnormal contrast sensitivity results and those who did not in the untreated group ($p > 0{\cdot}05$), suggesting that intraocular pressure level is a poor predictor of optic nerve fibre damage in patients with ocular hypertension.

An initial phase in chronic simple glaucoma may be identified when there is ocular hypertension (raised intraocular pressure (IOP) greater than 21 mmHg) but no observable pathological cupping of the optic disc and no glaucomatous field defect. Many ocular hypertensive patients never develop glaucoma, but others are in the early stages of the disorder.[1] If the latter patients are not treated, they will develop glaucomatous cupping of the optic disc and visual field defects. The number of patients who develop glaucoma from ocular hypertension has been estimated variously as 0·4%,[2] 0·5%,[1] 3·2%,[3] and 17·4%.[4] When the IOP is persistently above 31 mmHg the proportion of patients developing glaucoma is thought to be considerably higher, about 40%.[5] Thus patients with ocular hypertension, to a greater or lesser extent, appear to be more at risk of developing glaucoma than an age matched population with normal pressures.

It has been estimated that field loss may take 10 to 15 years to occur after the onset of raised pressure.[6] There is therefore a protracted period of time during which optic nerve fibre damage, currently undetectable in vivo, is occurring. Indeed, recent evidence from enucleated eyes has shown that there is optic nerve fibre loss in ocular hypertension in the absence of manifest field loss.[7] Clearly, more sensitive methods for differentiating between glaucomatous and non-glaucomatous ocular hypertensive patients are needed to provide specific criteria for diagnosis and therapy.

Many researchers have shown that spatial contrast sensitivity in glaucoma patients can be quite severely depressed[8-10] and that the reduction in sensitivity can be correlated with other measures of the progression and extent of the disease, such as field loss.[11] These losses of contrast sensitivity have been found even in patients with early glaucoma who show no central visual field abnormalities—that is, in the central 15°.[10] There is also some evidence to suggest that both contrast sensitivity[8,12] and colour vision may be impaired in patients with ocular hypertension.[13-15] Therefore it seemed a logical step to determine whether spatial contrast sensitivity is depressed in some ocular hypertensive patients but not in others. We used an accurate and reliable technique to measure contrast sensitivity[16] in order to determine its usefulness as an early test of nerve fibre loss in ocular hypertension.

Materials and methods

SUBJECTS

Patients with ocular hypertension were recruited as they presented to the Eye Clinic. Patients were diagnosed as ocular hypertensive if: (i) IOP was greater than or equal to 22 mmHg on at least two

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occasions in one or both eyes; (ii) there were normal optic discs on ophthalmoscopic examination; (iii) there were goniscopically demonstrated open anterior chamber angles[17]; (iv) there were full Topcon fields to isoptres I2e, I4e, and V4e. Patients were accepted on or off treatment.

Inclusion criteria. Patients were accepted for the study if (i) they fulfilled the above criteria for the definition of ocular hypertension; (ii) their spectacle correction was between −6·00 and +6·00 dioptres inclusive.

Exlusion criteria. Patients were excluded from the study if (i) there was evidence of concurrent eye disease; (ii) there was a personal history of any disorder which might give rise to eye disease in the future, for example diabetes; (iii) there was a diagnosis of glaucoma in the fellow eye.

Thirty patients with ocular hypertension were recruited, 20 males and 10 females. Seventeen patients had not received pressure reducing therapy during the previous three months (group 1) and 13 were receiving treatment (group 2). Details of these patients are summarised in Table 1.

GROUP 1

There were 12 male and five female patients not receiving medication with a mean age of 58·80 (SD 9·73) and 62·00 (SD 4·84) respectively. Eleven of the patients had bilateral ocular hypertension. The majority of the patients presented to Eye Clinic between one month and four years before recruitment, but three patients had been attending for seven, eight, and nine years.

GROUP 2

There were eight male and five female patients receiving treatment. Their mean ages were 60·75 (SD 8·01) and 63·20 (SD 12·26) respectively. Ten of the patients had bilateral ocular hypertension. Seven patients were on timolol (Timoptol), four were on adrenaline based eye drops, one was on timolol and epinephrine, and one was on pilocarpine. Six of these patients stopped treatment four days prior to the tests. Twelve patients presented to the Eye Clinic between one month and four years before recruitment; the remaining patient had been attending for 10 years.

All patients received a full ophthalmological examination including slit-lamp biomicroscopy, IOP readings recorded with the Goldmann applanation tonometer, and fundus examination. The end point for the measurement of IOP was taken as the mid point of the oscillation of the applanation prism.

VISION TESTS

All the patients had measurements of visual acuity, Topcon fields, and contrast sensitivity. In addition 11 patients had Octopus field tests.

Corrected distance visual acuity was measured at 6 metres with a Bailey-Lovie test chart.[18]

Visual fields were measured on a Topcon SBP-11H projection perimeter. The background illumination was 32·5 apostilbs and targets I2e, I4e, and V4e were used. Octopus fields were also obtained on some patients by means of programme 33, which assesses the central 30° of the visual field. The Octopus automatic field tester has a number of advantages when compaired to the Topcon perimeter. These include standardised testing conditions, static randomised presentations of the test targets, and numerical results to which statistical analysis can be readily applied.

For the contrast sensitivity test, static vertical sinewave gratings of variable spatial frequency were generated on a display oscilloscope by a two-channel microprocessor wave form generator,[19] which was addressed by a DEC PDP 11-23 computer. The contrast of the grating pattern was controlled by a digital to analogue converter on the computer. Contrast is defined as $(L_{max}-L_{min})/L_{max}+L_{min})$, where L is the luminance of a point on the screen. The procedure for obtaining contrast threshold measurements was based on the method of Wetherill[20] and has been described in detail elsewhere.[9 16]

Table 1 *Details of patients recruited for the study*

	No of patients	*Sex*		*Stopped treatment prior to tests*	*Bilateral OH*	*Unilateral OH*
		M	*F*			
Timolol	7	4	3	3	5	2
Adrenaline based medication	4	3	1	2	3	1
Timolol and epinephrine	1	1	—	1	1	—
Pilocarpine	1	—	1	—	1	—
No treatment	17	12	5	—	11	6
Total	30	20	10	6	21	9

OH=ocular hypertension

Table 2 *Intraocular pressure levels in the study groups*

Patient group	*No of patients*	*No of eyes*	*Grand mean IOP*	*SD*	*IOP at last visit*	*SD*
Group 1 (no treatment)	17	28	22·80	3·05	24·50	4·34
Group 2 (treatment)	13	23	22·05	2·16	21·30	2·56

Results

Monocular visual acuity in both patient groups ranged from 6/4 to 6/12 (mean 6/7·5). IOP readings are presented in Table 2. The grand mean pressure is the mean of all recorded pressures since the patient first attended the Eye Hospital. It can be seen from Table 2 that the only IOP measure which differed between the two groups was the group mean IOP at last visit. This result is attributable to the fact that one group was on pressure lowering therapy and the other was not.

A qualitative assessment of the cup to disc ratio was made. In 48 ocular hypertensive eyes this ratio was less than or equal to 0·5. Two of the remaining eyes had a ratio of 0·8 (same patient), and one eye had a ratio of 0·6, and thus one might have considered these eyes to be abnormal. However, in each case the discs were a good colour and the cups were circular, with a healthy rim of tissue at the disc margin. They were therefore considered to be colobomatous discs. Cup to disc ratios exceeded 0·5 in some eyes, which did not fulfil the eligibility criteria for ocular hypertension; details of the findings for these eyes are given in Table 4b.

The criterion for abnormal contrast sensitivity responses is based on our previous measurements of subjects (n=70), stratified by age, with normal vision.[14] Our technique of measurement was found to be reliable, with a correlation coefficient of 0·88 or better on a test/retest basis for each spatial frequency. In the present study a response was recorded as abnormal when one or more of the responses to the three spatial frequencies between one and six cycles per degree of visual angle (cpd) were more than two standard deviations (SD) from the age matched mean normal value. By this criterion 20 of the 28 eyes in group 1 and 12 of the 23 eyes in group 2 had abnormal

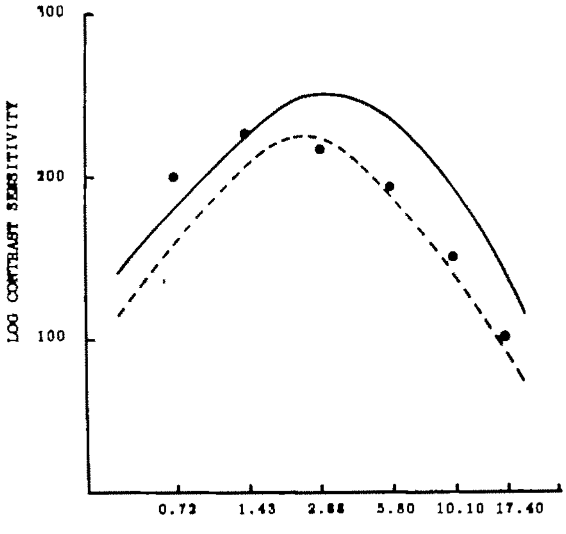

Fig. 1 *Contrast sensitivity values (●) for a 72-year-old ocular hypertensive patient with a mild reduction in sensitivity. Note that the area of greatest loss occurs in the middle of the spatial frequency range. ——= Mean contrast sensitivity value for age-matched control (71–75 years). ----= Two standard deviations from the mean*

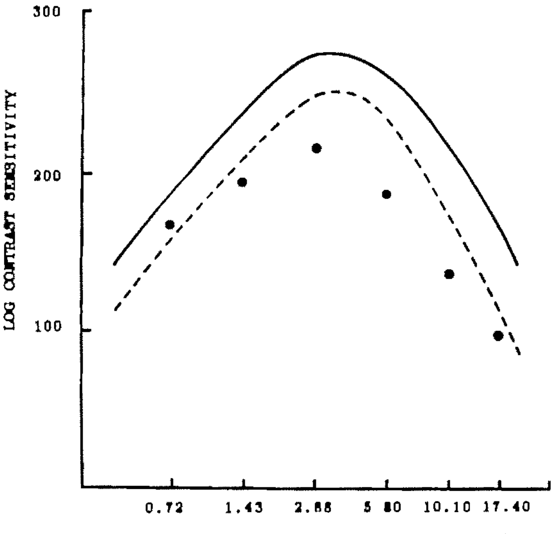

Fig. 2 *Contrast sensitivity values (●) for a 51-year-old ocular hypertensive patient with severe loss. The greatest reduction in sensitivity is still found at middle spatial frequencies, but note that a significant loss occurs over a much wider range of spatial frequencies ——= Mean contrast sensitivity value for age-matched control (51–60 years). ----= Two standard deviations from the mean.*

Table 3a *Contrast sensitivity (CS) results for both eyes of patients who had bilateral ocular hypertension*

Study group	*No of patients*	*CS results*
1	7	Both abnormal
1	3	Both normal
1	1	One abnormal, one normal
2	4	Both abnormal
2	4	Both normal
2	2	One abnormal, one normal

contrast sensitivity functions. Examples of the types of contrast sensitivity loss found in the study eyes are presented in Figs. 1 and 2.

Twenty-one patients had bilateral ocular hypertension. Only three of these patients produced asymmetrical contrast sensitivity results (Table 3a), where asymmetry was defined as a normal contrast sensitivity result in one eye and an abnormal result in the fellow eye. The optic discs of these three patients appeared symmetrical and had cup to disc ratios of 0·5, 0·4, and 0·2. The differences in grand mean IOP between right and left eyes did not exceed 2 mmHg.

The remaining nine patients fulfilled the eligibility criteria for entry to the study in one eye only. Of the nine fellow eyes four were normotensive. The other five eyes were excluded for various reasons. Four were ocular hypertensive but showed some narrowing of the superior rim of the optic disc, and one eye was normotensive but had a 2° nasal step. Such a small defect (<5°)[1] is not classically defined as glaucomatous. These patients were regarded as ocular hypertensive by the referring ophthalmologist on the basis of raised IOP and no visual field loss. However, we recognise the problems involved in including patients in whom the diagnosis of glaucoma is equivocal in one eye and not in the other. For this reason these patients should be distinguished from those who have no supportive evidence of optic nerve damage by disc and visual field change in either eye.

The results for these patients are presented in Table 3b. All but two of the above nine patients produced asymmetrical results. These two patients were also receiving treatment to both eyes. The first patient was on epinephrine 1% b.d. and had abnormal contrast sensitivity in the study eye but had symmetrical optic discs. The grand mean IOPs were 21 mmHg in both eyes. In the fellow eye a 2° nasal step was found on Topcon perimetry, as mentioned above, but normal contrast sensitivity. The second patient was on timolol 0·25% b.d. and had normal contrast sensitivity in the ocular hypertensive eye, but abnormal sensitivity in the fellow eye. The grand mean IOPs were 22 mmHg in both eyes, and the optic disc in the fellow eye had a cup to disc ratio of 0·6, with narrowing of the superior rim. If the eyes with suspicious discs and possible visual field defects are excluded, there remain four eyes which are normotensive. In each of them contrast sensitivity in the study and fellow eye was similar, with abnormal responses bilaterally in three patients and normal responses bilaterally in one patient. Thus IOP differences between the eyes were not reflected in this result.

Asymmetry between optic discs is usually con-

Table 3b *Contrast sensitivity (CS) results for both eyes of patients with unilateral ocular hypertension (OH)*

Patient	*Study group*	*CS result for OH eye*	*CS result for fellow eye*	*Reason for exclusion of fellow eye from study*
22	1	Abnormal	Abnormal	Suspect disc
28	1	Abnormal	Abnormal	Suspect disc
26	1	Abnormal	Abnormal	Normotensive
27	1	Abnormal	Abnormal	Normotensive
30	1	Abnormal	Abnormal	Normotensive
29	1	Normal	Normal	Normotensive
23	2	Abnormal	Normal	Possible VFD
25	2	Abnormal	Abnormal	Suspect disc
24	2	Normal	Abnormal	Suspect disc

Table 4a Contrast sensitivity (CS) results of bilateral ocular hypertensive patients who had asymmetrical optic discs

Patient	*Study group*	*Right eye*		*Left eye*	
		C/D ratio	*CS result*	*C/D ratio*	*CS result*
12	1	0·5	Normal	0·6	Normal
21	1	0·4	Normal	0·3	Normal
4	2	0·3	Abnormal	0·4	Abnormal
10	2	0·3	Abnormal	0·4	Abnormal

Table 4b *Contrast sensitivity (CS) results of unilateral ocular hypertensive patients who had asymmetrical optic discs*

Patient	*Study group*	*OH eye*		*Fellow eye*	
		C/D ratio	*CS result*	*C/D ratio*	*CS result*
26	1	0·4	Abnormal	0·6	Abnormal
27	1	0·3	Abnormal	0·1	Abnormal
28	1	0·3	Abnormal	0·6	Abnormal
22	2	0·3	Abnormal	0·6	Abnormal
24	2	0·4	Normal	0·6	Abnormal

sidered to be significant in the diagnosis of glaucoma.[1,21] Therefore we looked at the contrast sensitivity performance of nine patients who had optic disc cup asymmetry. The results are presented in Tables 4a and 4b. Interestingly, all but one patient produced symmetrical contrast sensitivity results. However, this paradoxical result may reflect the small cup to disc ratio differences between the two eyes or the qualitative aspect of the assessment rather than a genuine lack of correlation between optic disc appearance and contrast sensitivity.

An Octopus perimeter enabled us to perform automated field measurements on 13 eyes in 11 patients. However, even when this more rigorous procedure was used, the visual fields in 10 eyes were normal; the other three eyes showed early glaucomatous field defects. These defects were relative arcuate scotomata, in each case adjoining the blind spot. In two of the three eyes Octopus field testing revealed increased thresholds in the foveal area. In these three eyes contrast sensitivity was abnormal (Table 5). The three patients with Octopus field defects were in group 1 (no treatment). In two of the cases the IOPs (both the grand mean and the IOP recorded on the day of the test) were only marginally raised, the highest reading being 23·5 mmHg. The third patient was found to have pressures of 36 and 28 mmHg in the right and left eyes respectively and he was placed on timolol drops 0·5% b.d. to both eyes.

It might be argued that the reason for the high proportion of patients with abnormal contrast sensitivity was poor selection, and that if a more rigorous visual field criterion had been used some patients would have been diagnosed as having chronic simple glaucoma. The above mentioned results from an Octopus automated perimeter on a sample of the eyes included in the study show that this is unlikely to have been the case.

The relationship between contrast sensitivity and the grand mean IOP was examined. In the untreated group there was no significant difference between the mean IOPs of the 20 eyes with reduced sensitivity and the eight which produced normal responses ($t=0{\cdot}199$, df=26, $p>0{\cdot}05$). In the treatment group 12 eyes produced attenuated contrast sensitivity responses, and 11 were within normal limits. Again, differences in grand mean IOPs for the two responses were not statistically significant ($t=1{\cdot}8757$, df=21, $p>0{\cdot}05$).

Table 5 *Contrast sensitivity (CS) and visual field results of patients who had Octopus perimetry*

	Normal CS	*Abnormal CS*
Normal Octopus fields	1	9
Abnormal Octopus fields	0	3

Discussion

In this study 63% (32 eyes) of the ocular hypertensive eyes showed an impairment of central spatial contrast sensitivity. Individual loss of contrast sensitivity was not related to the grand mean IOPs, and a number of patients with unilateral ocular hypertension who had consistently normotensive fellow eyes nevertheless showed impaired contrast sensitivity in both eyes.

It is accepted that some patients with ocular hypertension will develop chronic simple glaucoma. Those patients with higher pressures (for example, greater than 30 mmHg) do appear to be at greater risk of developing manifest chronic simple glaucoma,[5] but when all levels of raised IOP are considered the number of ocular hypertensive patients developing chronic simple glaucoma is surprisingly low.[22] However, until criteria exist for determining which patients are likely to suffer visual damage, all patients with raised IOP have to be considered at risk.

More than half of our ocular hypertensive patients had defective contrast sensitivity. 71% of eyes in group 1 and 52% in group 2 performed at a level which was more than 2 SDs from the age matched norm for one or more spatial frequencies. These abnormal results were obtained from eyes with good visual acuity and full Topcon fields. Surprisingly, of the 11 patients who had Octopus field tests (a more rigorous method of field testing) only three were found to have changes which might be indicative of glaucoma. Both the contrast sensitivity test and the

Octopus field test sample the central 10–15° of vision, but it appears that contrast sensitivity is the more sensitive measure of function for central retina.

It is apparent from our results that a far greater proportion of our patients showed reduced contrast sensitivity (and, presumably, optic nerve damage) than might have been expected on the basis of previous reports.[8-12] One reason for this discrepancy might be that our control population, used for aged matched comparisons, was not representative. In the present study the comparisons are based on a control population of 70 subjects (31 male and 39 female) stratified by age.[16] Moreover, these control data have been supplemented by data from a further 100 normal subjects whose contrast sensitivities fall well within the limits defined by the earlier population. It seems likely, therefore, that in the standardised conditions of the present study a depression of sensitivity greater than 2 SDs below the mean is likely to represent abnormality.

An alternative explanation is that some aspect of the selection of our ocular hypertensive group, either the inclusion/exclusion criteria or the way in which patients were referred, meant that our patients were more at risk of developing optic nerve damage than another group of ocular hypertensive patients not selected in the same manner. This is a possibility, though we have been unable to determine what aspect of the selection/referral procedure could account for our results.

Early glaucomatous defects are typically thought to occur outside the central 5–10° of the visual field.[23] However, there is increasing evidence suggesting that vision in central retina is abnormal in ocular hypertension and early glaucoma. Colour vision defects which involve central vision have been reported in ocular hypertension by Lakowski *et al.*[13] and in glaucoma and ocular hypertension by Fishman *et al.*[14] and Adams *et al.*[15] Depression of foveal sensitivity and a generalised depression of the whole central field in patients with ocular hypertension have been reported by Lichter and Standardi[24] and Anctil and Anderson.[25] Our own results confirm that depression of central visual thresholds can occur in ocular hypertension, and we suggest that this should be taken as evidence of early optic nerve fibre damage.

The psychophysical data are supported by the in-vitro work of Quigley *et al.*,[7] who examined the relationship between visual field defects and optic atrophy demonstrated by histology. The histological examination was carried out on enucleated eyes ante or post mortem. Definite focal losses of ganglion cells and optic nerve fibres were found in cases of eyes suspected of having glaucoma even though perimetry had demonstrated no field loss in vivo. The decrease in the total number of nerve fibres below the mean control number varied from 12% to 40% in these patients.

In the presence of glaucoma one might expect the eye with the more advanced cupping or visual field defect to have a greater loss of contrast sensitivity. Such an association has been reported by Atkin *et al.*[12] and Ross[11] in glaucoma patients. One might also expect there to be a relationship between IOP and contrast sensitivity loss. In our ocular hypertensive patients no association of this kind was found. All but three patients with bilateral ocular hypertension (85%) produced symmetrical contrast sensitivity results (that is, both eyes were either normal or abnormal) despite the fact that in most cases there were pressure differences between the patients' right and left eyes. It is also surprising that seven of the nine patients in whom only one eye satisfied the criteria for ocular hypertension produced symmetrical results, since four of these seven had normotensive fellow eyes and three of these four produced abnormal results. From the point of view of screening, infrequent IOP measurements alone may be a poor indicator of the existence of optic nerve fibre damage. When considering the cause of optic nerve fibre damage in normotensive fellow eyes the inference may be that periods of raised pressure in the fellow eyes have been missed.

From these findings it is clear that contrast sensitivity detects visual loss earlier than rigorous field testing. It is therefore unwise to assume that optic nerve fibres in ocular hypertensive eyes are undamaged if the visual field appears to be full. Our results suggest that the value of ocular pressure measurement for predicting early optic nerve damage is limited, though its use as part of a battery of clinical tests is still important.

Traditionally clinicians do not put a patient on to treatment on the basis of raised IOP alone, unless the pressure is very high (for example, >30 mmHg). Usually more emphasis is placed on optic disc appearance and perimetry. In this study we found that there was no obvious relationship between the level of IOP over a wide range and contrast sensitivity loss in either group. This result was hardly surprising in the case of group 2, because, if therapy is effective, the IOP of all of the treated patients should be within normal limits irrespective of the progression of the disease. However, the finding that there is no significant difference in mean IOP between *untreated* patients who appear to have visual loss and those who do not is very interesting, and shows that IOP measurement, over a wide range, is a very poor indicator of optic nerve fibre damage. It confirms that the policy of not treating patients on the basis of IOP alone is prudent. However, our contrast sensitivity results on patients with normal discs and fields show that, if treatment is delayed until manifest signs can be observed (that is, disc changes and/or field defect), extensive visual loss may already have taken place. This is reinforced by recent histopathological studies.[7]

In this study we investigated a group of patients with raised ocular pressure but with no observable optic disc changes and no field loss. This appears to be a uniform group and, with the exception of patients with very high pressures, the clinician has no specific criterion for treating some patients and not treating others. Our test divides these patients into two groups, those with normal contrast sensitivity and those with abnormal contrast sensitivity. We believe that reduced contrast sensitivity reflects early optic nerve damage and that contrast sensitivity measurements might therefore be used as a criterion for therapy in ocular hypertension.

It has not yet been demonstrated directly that contrast sensitivity is a valid measure of optic nerve damage. However, this could be done simply by a longitudinal study of ocular hypertensive patients. At the same time it would also be interesting to see whether treatment of these patients with pressure reducing therapy is effective in halting and possibly reversing any optic nerve damage that may be occurring, shown by contrast sensitivity loss.

Until such a study has been carried out, we feel it is very important that patients who are referred with raised IOP should undergo rigorous tests of central vision, such as contrast sensitivity and colour vision, in addition to routine visual field testing.

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Albinism with haemorrhagic diathesis: Hermansky-Pudlak syndrome

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SUMMARY Four cases of albinism with haemorrhagic diathesis (Hermansky-Pudlak syndrome) are presented. The cases displayed wide phenotypic variation. Electroretinography was performed on all four patients and was found to be normal. One patient developed a cutaneous malignant melanoma.

Albinism associated with a haemorrhagic diathesis and the systemic accumulation of a ceroid-like substance (the Hermansky-Pudlak syndrome) was first described in detail in two albinos who suffered recurrent attacks of bleeding.[1] It has since been reported in diverse ethnic populations, and about 200 cases have now been reported or are known to exist.[2] Although rare, it is particularly prevalent in Puerto Ricans, and there is a higher than average incidence in people from southern Holland.[3] The condition is inherited as an autosomal recessive trait, but in common with other rare recessive conditions it may show pseudodominance in populations with a high gene frequency.

We report here four cases which demonstrate the wide phenotypic expression of this condition and include electroretinographic (ERG) studies, the techniques having been fully described previously.[4] One of the patients developed a cutaneous malignant melanoma.

Case reports

CASE 1

A 38-year-old female presented with marked generalised hypopigmentation, reduced visual acuity, and photophobia (Fig. 1). She has always bruised easily, and she bled excessively during appendicectomy and after dental extractions. In 1964 she underwent ligation of an external carotid artery in an attempt to control recurrent and severe epistaxis. The epistaxis continued subsequently, but appeared to be controlled by oestrogen therapy. In 1978 she underwent surgery to remove an acoustic neuroma. Her parents are unrelated, and a younger brother is unaffected.

Her visual acuities are 6/60 in each eye. She has an obvious horizontal nystagmus and an esotropia. Her blue irides are markedly translucent (Fig. 2) and she

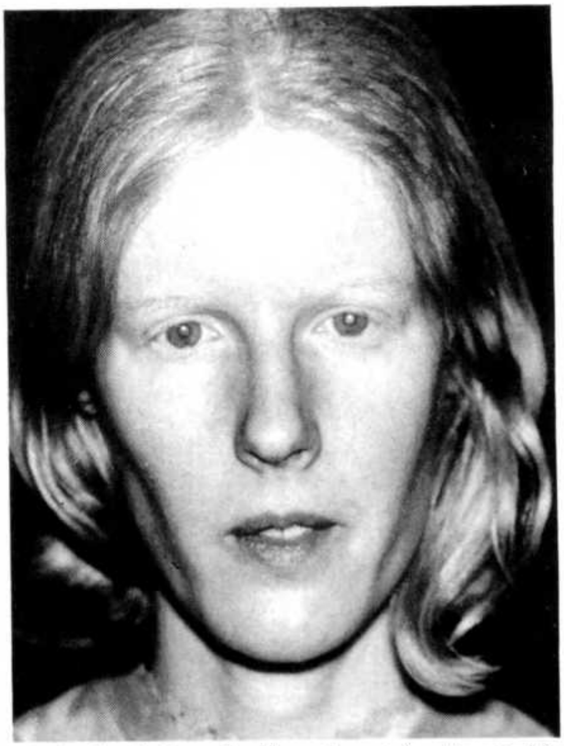

Fig. 1 *Case 1. Generalised hypopigmentation characteristic of an albino.*

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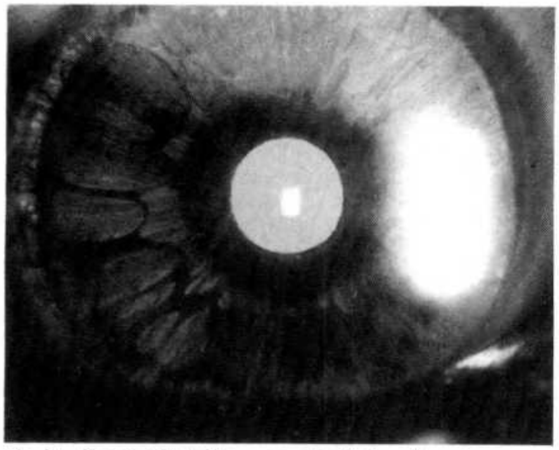

Fig. 2 *Case 1. The irides are markedly translucent.*

does not have any discernible fundus pigmentation. Her ERG showed normal responses.

This case has previously been reported.[5,6] She was found to have a platelet storage pool defect with prolonged bleeding time and abnormal aggregation studies. The bone marrow was examined, but no ceroid pigment inclusions were found within macrophages. Mackie and his coworkers[7] reported the use of platelet transfusion, cryoprecipitate, and factor VIII concentrate to achieve haemostasis during the surgery for removal of the acoustic neuroma.

CASE 2

A 29-year-old female of southern Italian extraction with light brown skin and dark brown hair had reduced visual acuity and photophobia. She had bruised very easily all her life. After dental extraction bleeding usually continued for 24 hours, and bleeding continued for a week after tonsillectomy at the age of 9 years. Her parents are first cousins and she has one sister with the same condition (case 3).

Her corrected visual acuities are 6/60 in each eye. She has hypermetropic astigmatism, horizontal nystagmus, and marked esotropia. Her irides are brown with moderate translucency and her fundi are hypopigmented. Her single stimulus ERG showed normal oscillatory potentials.

Her template bleeding time was prolonged, with normal prothrombin time (PT), partial thromboplastin time with kaolin (PTTK), and platelet count. There was a severe platelet release defect with low ADP and increased ATP/ADP ratio (adenosine tri-/diphosphate). Bone marrow studies were not performed.

CASE 3

The 23-year-old sister of case 2 is of similar colouring, with light brown skin and dark brown hair (Fig. 3), and has a reduced visual acuity and photophobia. She has suffered from marked spontaneous bruising all her life.

Her corrected visual acuities are 6/60 in each

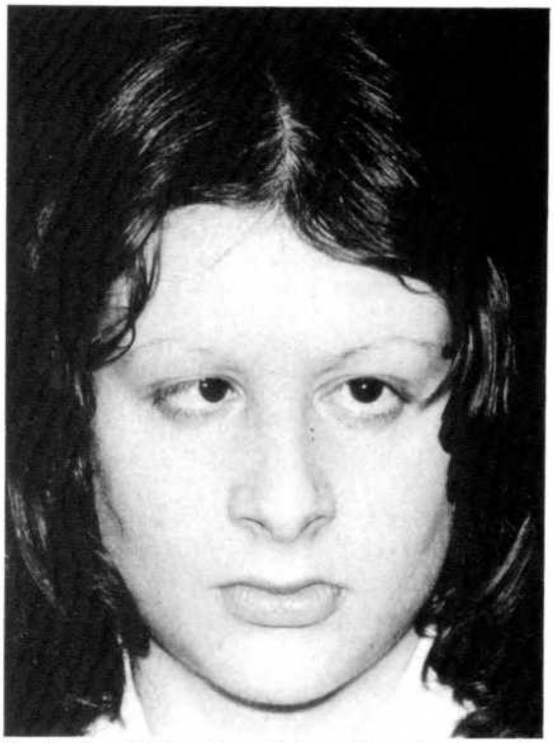

Fig. 3 *Case 3. The skin and hair are lighter than is usual in Southern Italians, and an esotropia is present.*

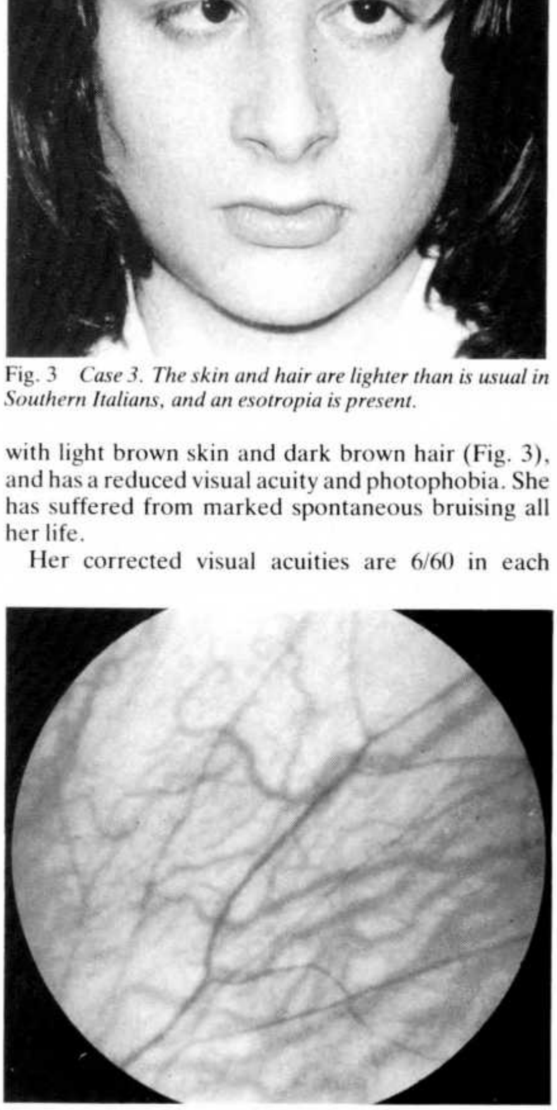

Fig. 4 *Case 3. The hypopigmented fundus.*

eye. She has hypermetropic astigmatism, horizontal nystagmus, and esotropia. Her irides are brown, with moderate translucency, and her fundi are hypopigmented (Fig. 4). Her single stimulus ERG showed normal oscillatory potentials.

Her template bleeding time was prolonged. Her PT, PTTK, and platelet count were within normal limits. A platelet release defect was present, with low ADP and an increased ATP/ADP ratio. Her bone marrow showed abnormal ceroid pigment inclusions within macrophages.

CASE 4

A 58-year-old male has pale skin and light blond hair, reduced visual acuity, and photophobia. He has had a life-long history of a marked tendency to bleed. He bleeds for at least 24 hours after dental extraction. In 1960 he underwent excision of a malignant melanoma of his leg with block dissection of the regional lymphatic nodes; surgery was prolonged owing to excessive bleeding. He is in good health with no pulmonary or bowel symptoms. A chest x-ray was normal. His parents were unrelated, and he has an unaffected brother, sister, and two daughters.

His corrected visual acuities are 6/60 in each eye. He has a moderate horizontal nystagmus and an exotropia. His irides are hazel and are markedly translucent. He has no discernible fundus pigmentation. His single stimulus and flicker ERGs were normal, with normal oscillatory potentials. (Fig. 5).

His template bleeding time was prolonged, and his PT and PTTK were within normal limits. A marked

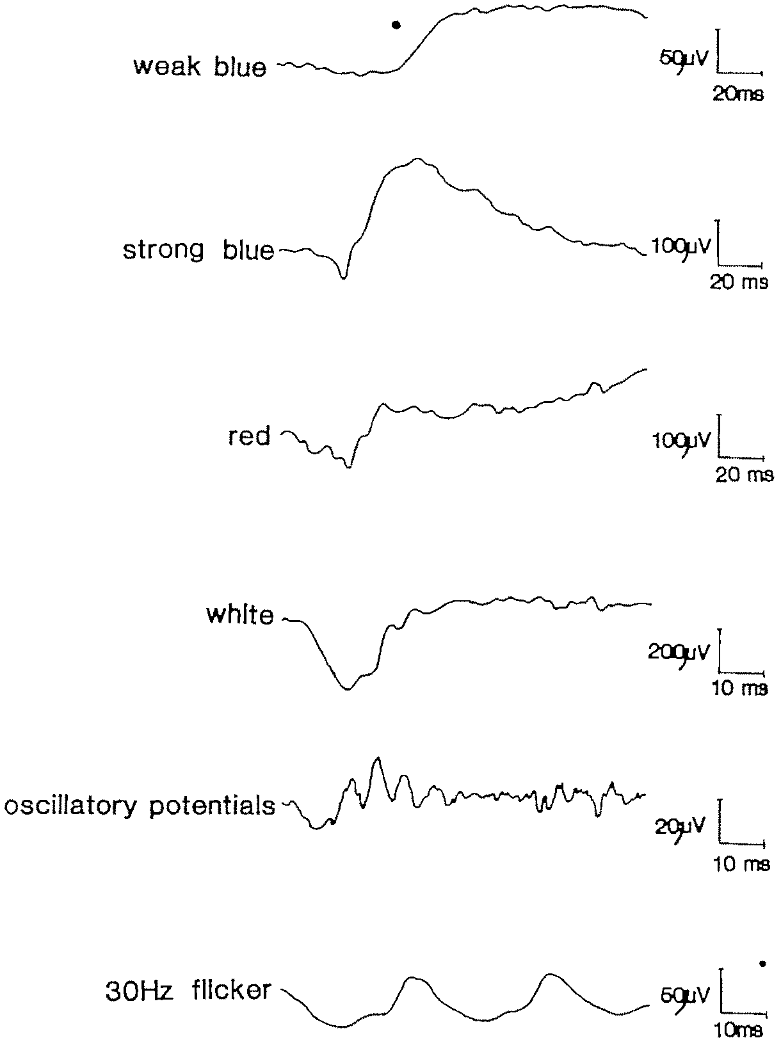

Fig. 5 *Case 4. Normal single stimulus and flicker ERGs are present, as are normal oscillatory potentials.*

platelet release defect, associated with deficient storage pool ADP, was present. Bone marrow studies showed occasional pigment laden macrophages.

Discussion

The Hermansky-Pudlak syndrome is one of the tyrosinase-positive forms of oculocutaneous albinism.[8] There is wide variation in the phenotypic expression of the condition, which is largely dependent on the constitutional (racial) pigmentary background of the individual. The four cases presented vary from the typical appearance of an albino (case 1, Fig. 1) to the dark haired sisters (cases 2 and 3, Fig. 3) who would not readily be recognised as being albinos. Garay and his coworkers[9] reported that four of their cases, all Puerto Ricans, had been treated at various teaching hospitals without the diagnosis of albinism being made.

The ocular features of this condition are similar to those of the more common form of tyrosinase-positive oculocutaneous albinism.[10] There is markedly reduced visual acuity, nystagmus, and a high incidence of strabismus. The irides are translucent, the fundi hypopigmented, and foveal hypoplasia is present.

The bleeding diathesis is usually mild and is commonly brought to notice by dental extraction. However, several fatalities from haemorrhage have been reported.[3 11] The diathesis is due to a platelet defect of the storage pool type.[6] There is an absolute deficiency of dense bodies within platelets, the dense bodies being storage organelles for nucleotides and serotonin. The platelets fail to undergo the release reaction, and therefore there is no secondary phase of irreversible aggregation.[12] Aspirin and related drugs such as indomethacin, which also impair platelet aggregation, should be avoided by these patients, as a mild bleeding tendency may be exacerbated.[13]

A third part of the triad is the accumulation of ceroid-like material in reticuloendothelial cells and other tissues.[1 14 15] The recently reported pulmonary and gastrointestinal manifestations of this condition are probably related to this abnormal accumulation within tissues. The development of restrictive lung disease in the third and fourth decades due to a fibrosing alveolitis has been reported by various authors.[9 16 17] An ulcerative form of colitis has been reported in Puerto Rican patients with this condition.[9 18]

Abnormal electroretinographic findings have been reported in two cases with the Hermansky-Pudlak syndrome.[19] It was suggested that the reduced rod and cone responses may have been caused by accumulation of the ceroid-like material within the retina. The ERGs in our four patients were normal. We are therefore unable to confirm the previous report.[19] This may be due to underlying genetic diversity in otherwise phenotypically similar cases.

There have been several reports of malignant melanomas developing in patients with albinism[20-25] Witkop *et al.*[2] consider that melanomas may not have a higher incidence in albinos than in the general population. We here report a malignant melanoma in a patient with the Hermansky-Pudlak syndrome (case 4).

We are indebted to Professor Barrie Jay for encouragement in studying these patients, and to Professor G B Arden for advice on the retinal electrophysiological studies

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Stimulation of dopamine receptors (type 2) lowers human intraocular pressure

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SUMMARY The interaction between bromocriptine and metoclopramide on intraocular pressure (IOP), pupil diameter, and other parameters were studied in healthy volunteers. Pupil diameter was not affected by both treatments and only bromocriptine lowered IOP. Prior treatment with metoclopramide blocked the IOP-lowering effect of bromocriptine. It is concluded that bromocriptine lowers IOP by stimulation of dopamine-2 receptors.

Oral bromocriptine (1·25 mg single dose) lowers intraocular pressure (IOP) in healthy volunteers without affecting blood pressure or pupil diameter.[1] Topical bromocriptine lowers IOP without affecting pupil diameter or prolactin levels.[2] Bromocriptine has dopamine 2 (DA2) receptor agonist and dopamine 1 (DA1) and alpha adrenoceptor blocking actions.[3,4] Metoclopramide (a substituted benzamide) is a specific DA2 receptor antagonist.[5,6] We planned to study the effects of these two compounds alone and in combination in healthy volunteers on IOP, serum prolactin, pupil diameter, heart rate, and blood pressure to evaluate the interaction between them and to try to find which property of bromocriptine lowers IOP.

Materials and methods

Eight healthy male volunteers participated in this study. None wore contact lenses. They attended on four occasions, at least seven days apart, at the same time of the day (10·30–11·00 am) to receive either metoclopromide (10 mg) or matched placebo intravenously followed (15 minutes later–time zero) by either bromocriptine (1·25 mg) or a matched placebo tablet orally in a randomised double blind balanced design on the basis of two four-by-four Latin squares. They arrived fasting, and nothing except water to quench thirst was allowed until two hours after dosing, when a light meal was provided.

Pupil diameter, radial pulse rate, blood pressure (sitting), intraocular pressure, and prolactin level were measured in that order, before and at 1, 2, 3, and 4 hours after the subject took the tablet. Pupil diameter was measured by a pupil gauge,[7] blood pressure by a Hawksley random zero sphygmo manometer, intraocular pressure by non-contact tonometery,[8,9] and serum prolactin levels by radioimmunoassay.

Volunteers were asked to report any subjective adverse effects. Diazepam and procyclidine were available to treat dystonic reactions if they occurred.

The IOP, pupil diameter, heart rate, and blood pressure readings were analysed by calculating the area under the response versus time curve for each subject and on each treatment. These were then analysed by multiple regression analysis after $\log_e$ transformation to normalise the distribution of the residuals. The areas under the curves for serum prolactin calculated as above were not normally distributed and were therefore analysed by Freidman's two-way analysis of variance. Paired comparisons were then done by the Mann-Whitney test.

Results

Significant effects were observed on the IOP (Fig. 1). In comparison with the placebo the IOP was significantly reduced in both eyes (right eye $p<0\cdot04$, left eye $p<0\cdot01$) only when bromocriptine alone was given. This effect was abolished by pretreatment with metoclopramide, which alone had no effect on the IOP. There were no significant changes in pupil diameter, blood pressure, or heart rate.

Analysis of serum prolactin showed a significant effect of treatment ($p<0\cdot01$) (Fig. 2). The effect of all treatments was significantly different from that of placebo. Bromocriptine inhibited the secretion of prolactin ($p<0\cdot05$), and this response was again

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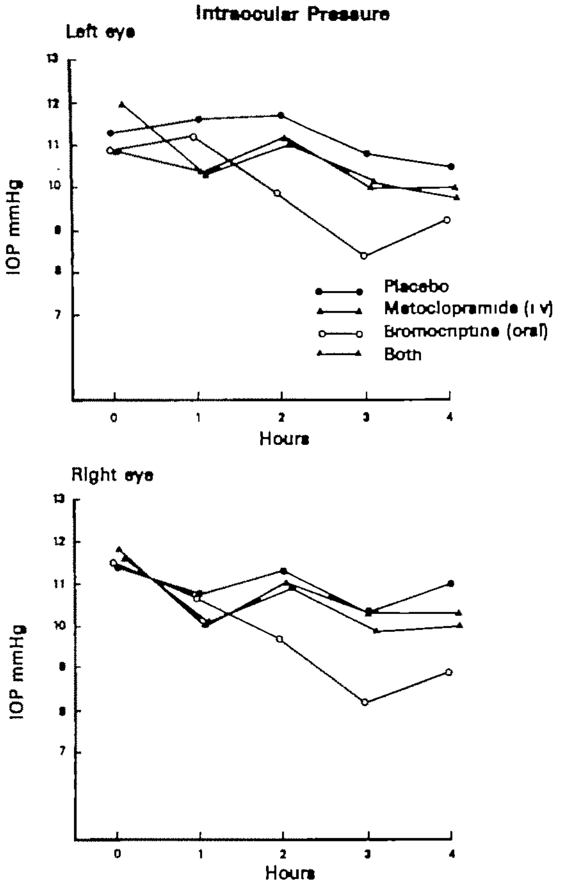

Fig 1 *Mean values of IOP (mmHg).*

abolished by pretreatment with metoclopramide, which caused a significant increase in prolactin levels both when given alone and in combination with bromocriptine ($p<0{\cdot}01$); the difference between these two responses was not significant.

Discussion

The absence of changes in pupil diameter in this study makes unlikely the possibility that the IOP was reduced through alpha adrenoceptor blockade by bromocriptine or the cholinergic effect[10] of metoclopramide.

The changes in prolactin levels show that the dose of metoclopramide used was enough to block the effect of bromocriptine totally; in fact the difference between the responses to metoclopramide with and without bromocriptine was not significant. This was accompanied by a total abolition of the ocular hypotensive effect of bromocriptine. If the IOP-lowering effect of bromocriptine was, totally or partially, due to inhibition of DA1 receptors, we should expect a lowered IOP after treatment with the combination of bromocriptine and metoclopramide, which did not occur. We therefore conclude that stimulation of DA2 receptors in man lowers IOP.

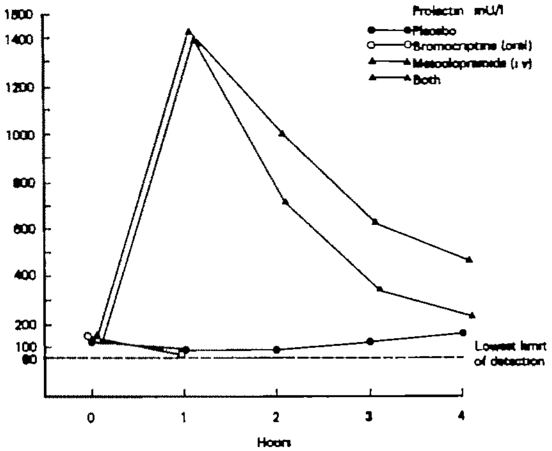

Fig 2 *Mean values of serum prolactin (mU/l).*

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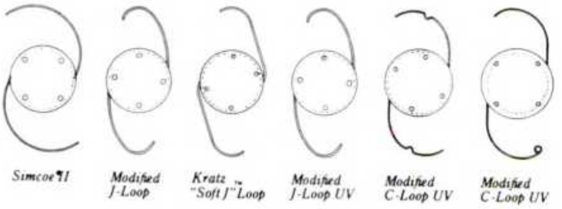

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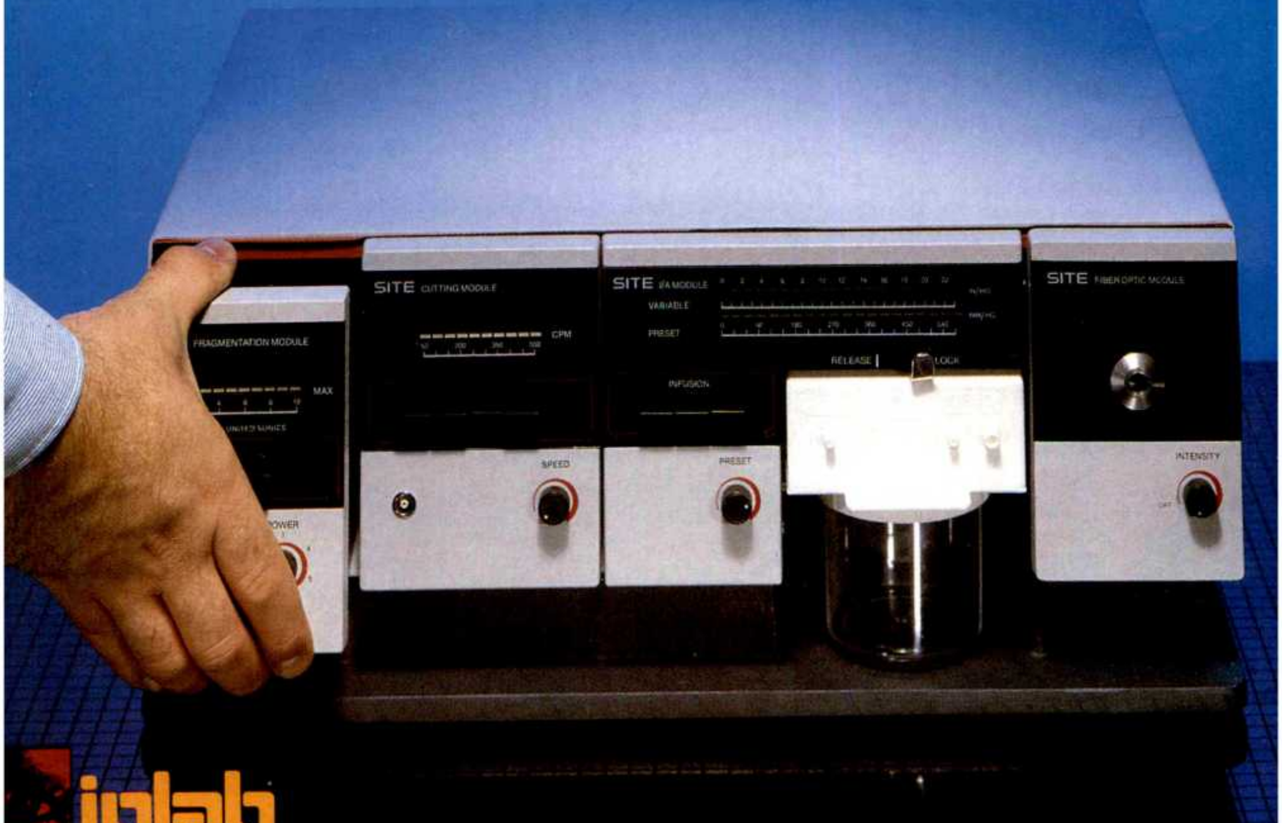

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Vitreous haemorrhage after cataract extraction

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SUMMARY One hundred eyes undergoing intracapsular cataract extraction and 100 undergoing extracapsular extraction were examined prospectively within one week postoperatively and again at 6–10 weeks postoperatively. Indirect ophthalmoscopy showed vitreous haemorrhage in 36% of the intracapsular group and 13% of the extracapsular group. Vitreous haemorrhage was significantly related to the occurrence of operative hyphaema ($p<0.01$) but not to iridectomy ($p>0.5$). In the intracapsular group the use of chymotrypsin significantly reduced the incidence of vitreous haemorrhage ($p<0.01$). Three different types of vitreous haemorrhage were identified—streaks, diffuse haze, and beads in the vitreous base. Wound haemorrhage and operative hyphaema account for most cases, but it is suggested that zonular traction may be responsible for the bead haemorrhages and also for the retinal haemorrhages reported by other authors. Although no difference in visual result or incidence of cystoid macular oedema was observed in this study, a relationship to the vitreoretinal pathology of aphakia is suggested.

Vitreous haemorrhage after cataract extraction has been considered an uncommon complication resulting from primary or secondary wound haemorrhage or less commonly from the iridectomy.[1] Small amounts of blood are easily overlooked in the early postoperative period, though peripheral retinal haemorrhages in aphakic eyes are well documented.[2,3] Larsson and Osterlin[4] have suggested that zonular traction on peripheral retinal vessels may cause extravasation during lens extraction. We examined the incidence and significance of blood in the vitreous prospectively after cataract extraction in a group of 200 clinic patients, and attempted to correlate the morphological appearance of the haemorrhage with its possible origin.

Subjects and methods

Patients admitted for cataract extraction to any of three hospitals—Royal Perth Hospital, Sir Charles Gairdner Hospital, and Fremantle Hospital—were recruited in a random manner over a two-year period. The only selection criterion was availability for follow-up. Surgery was performed by one of 20 ophthalmologists or house staff using varied intracapsular or extracapsular techniques.

The operative details and results of follow-up examination within the first week and again six to 10 weeks postoperatively were recorded prospectively. At each postoperative check slit-lamp examination and indirect ophthalmoscopy after maximal dilation were performed. The best corrected acuity was recorded and a three-mirror lens examination performed if cystoid macular oedema was suspected. Fluorescein angiography was not carried out as part of this study. Recruitment stopped after 100 cases of both intracapsular and extracapsular extractions. Fifty of those having extracapsular extractions also had a Sinsky style posterior chamber lens inserted as a primary procedure.

A separate group of six phakic eyes with hyphaema following routine trabeculectomy were examined to determine whether blood could pass through the intact zonule.

The data were analysed by the χ^2 test with Yates's modification.

Results

The mean age of the patients was 71 years with a range of 12 to 95 years.

36% of eyes undergoing intracapsular surgery and 13% undergoing extracapsular surgery were found to have some degree of vitreous haemorrhage (Table 1). This is a statistically significant difference

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Table 1 *Incidence of vitreous haemorrhage after cataract extraction (expressed as a percentage)*

	Postoperative visual acuity 6/12 or better %	*Vitreous haemorrhage detected* %	*Surgical hyphaema* %	*Iridectomy* %
Intracapsular (n=100)	59	36	35	98
Extracapsular (n=100)	69	13	9	15
Extracapsular subgroup without IOL (n=50)	68	18	14	27
Extracapsular subgroup with IOL (n=50)	70	8	4	2

($\chi^2=13$; $p<0{\cdot}01$). The blood was commonly seen in small streaks in the inferior vitreous anteriorly (type 1) and was often accompanied by a diffuse haze in the inferior vitreous (type 2) (Fig. 1). Small beads of blood, single or multiple, were seen in the vitreous base (type 3), usually associated with an otherwise clear vitreous. All three types occurred together in some eyes (Fig. 1).

The incidence of operative hyphaema was 60% with intracapsular extraction but only 9% with extracapsular extraction. Most surgeons performing intracapsular extraction also employed conjunctival flaps, large white limbus incisions, and peripheral iridectomies, while the majority of surgeons performing extracapsular extractions used clear corneal sections, with no iridectomy when an intraocular lens was inserted. Sixty-four operative hyphaemas were attributed to wound haemorrhage, and five to the iridectomy. In the intracapsular group vitreous haemorrhage was significantly more common ($\chi^2=9{\cdot}1$; $p<0{\cdot}01$) after surgical hyphaema (55%) than without it (25%). In the extracapsular group vitreous haemorrhage occurred in 45% of the group with surgical hyphaema and 12% of those without it. This difference is also significant ($\chi^2=25$; $p<0{\cdot}01$).

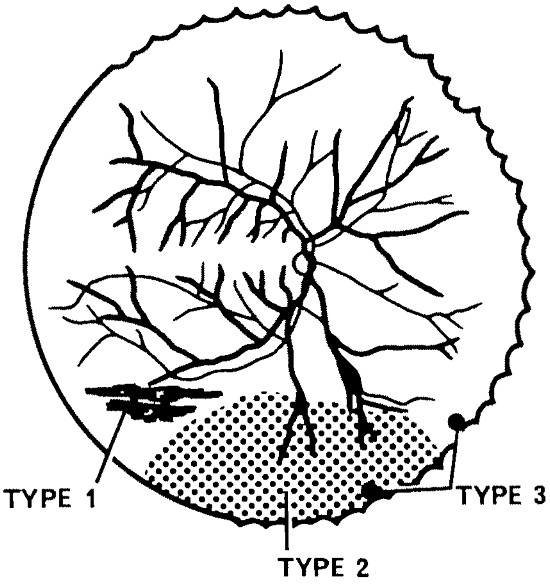


Fig. 1 *Diagram showing types of vitreous haemorrhage observed after cataract extraction.*

The finding of blood in the peripheral vitreous was also related to the quality of the fundus view obtained. In the intracapsular group the ora could be seen through 360° with a 28 D lens without scleral depression in 48% of cases. In 25% of cases the ora could be seen in only one quadrant by this method. The incidence of vitreous haemorrhage in the 25 cases with a poor quality view was only 4%, whereas in the other 75 it was 56%, which is a significant difference ($\chi^2=8{\cdot}0$; $p<0{\cdot}01$).

In the extracapsular group without an intraocular lens (IOL) a good 360° view of the ora was easily obtained in 32%, while of those with an IOL it was possible in only 26% in the early postoperative period. Blood was detected in nine cases without an IOL but only in four cases with an IOL.

In those intracapsular cases in which no surgical hyphaema occurred the use of chymotryspin was significantly associated with a decreased incidence of vitreous haemorrhage ($\chi^2=6{\cdot}7$; $p<0{\cdot}01$). There was no significant relationship between vitreous haemorrhage and either cystoid macular oedema ($\chi^2=2{\cdot}1$; $p>0{\cdot}05$) or worse than 6/12 best corrected vision ($\chi^2=2{\cdot}7$; $p>0{\cdot}05$) in the intracapsular group at follow-up. The vitreous face was ruptured immediately postoperatively in 24% of the intracapsular group but in 32% at follow-up. Rupture of the vitreous face was not related to the use of chymotrypsin ($\chi^2=0{\cdot}4$; $p>0{\cdot}05$) or the finding of cystoid macular oedema ($\chi^2=1{\cdot}1$; $p>0{\cdot}05$). Of the intracapsular group 59% achieved 6/12 or better at follow-up, and 12% had cystoid macular oedema. Nineteen eyes had an unrelated cause of poor vision other than cataract diagnosed preoperatively.

In the extracapsular group 68% without an IOL had a best corrected acuity of 6/12 or better, and 70% of those with an IOL had 6/12 or better. 10% in each group had cystoid macular oedema diagnosed biomicroscopically. Fifteen of the 100 extracapsular cases had a known cause of poor central vision other than cataract diagnosed preoperatively. Among those of the extracapsular group in whom no wound haemorrhage occurred the presence of a surgical iridectomy was not significantly related to the finding of vitreous haemorrhage ($\chi^2=4\cdot6$; $p>0\cdot05$).

Of note were two eyes that had previously undergone trabeculectomy and iridectomy. One had an intracapsular extraction and the other an extracapsular extraction, but both had small beads of haemorrhage over the ora postoperatively. These findings prompted an examination of a group of six phakic eyes in which trabeculectomy had been complicated by hyphaema. In two of these blood was seen in the inferior vitreous. During the study only one secondary wound haemorrhage was detected, and this was excluded from the study because further surgery was required.

In several eyes small intraretinal dot haemorrhages were seen near the ora with three-mirror examination, but because this examination was not possible in all cases this type of haemorrhage was excluded from the findings analysed.

Discussion

Small amounts of blood are common in the peripheral vitreous after recent cataract surgery and frequently occur with hyphaema. The finding that blood can be found in the inferior vitreous after surgical hyphaema in some phakic eyes supports the contention that blood may pass through the intact zonule. Furthermore vitreous haemorrhage can be found in 27% of traumatic hyphaemas when routinely assessed.[5] However, not all surgical hyphaemas lead to vitreous haemorrhage even after intracapsular extraction.

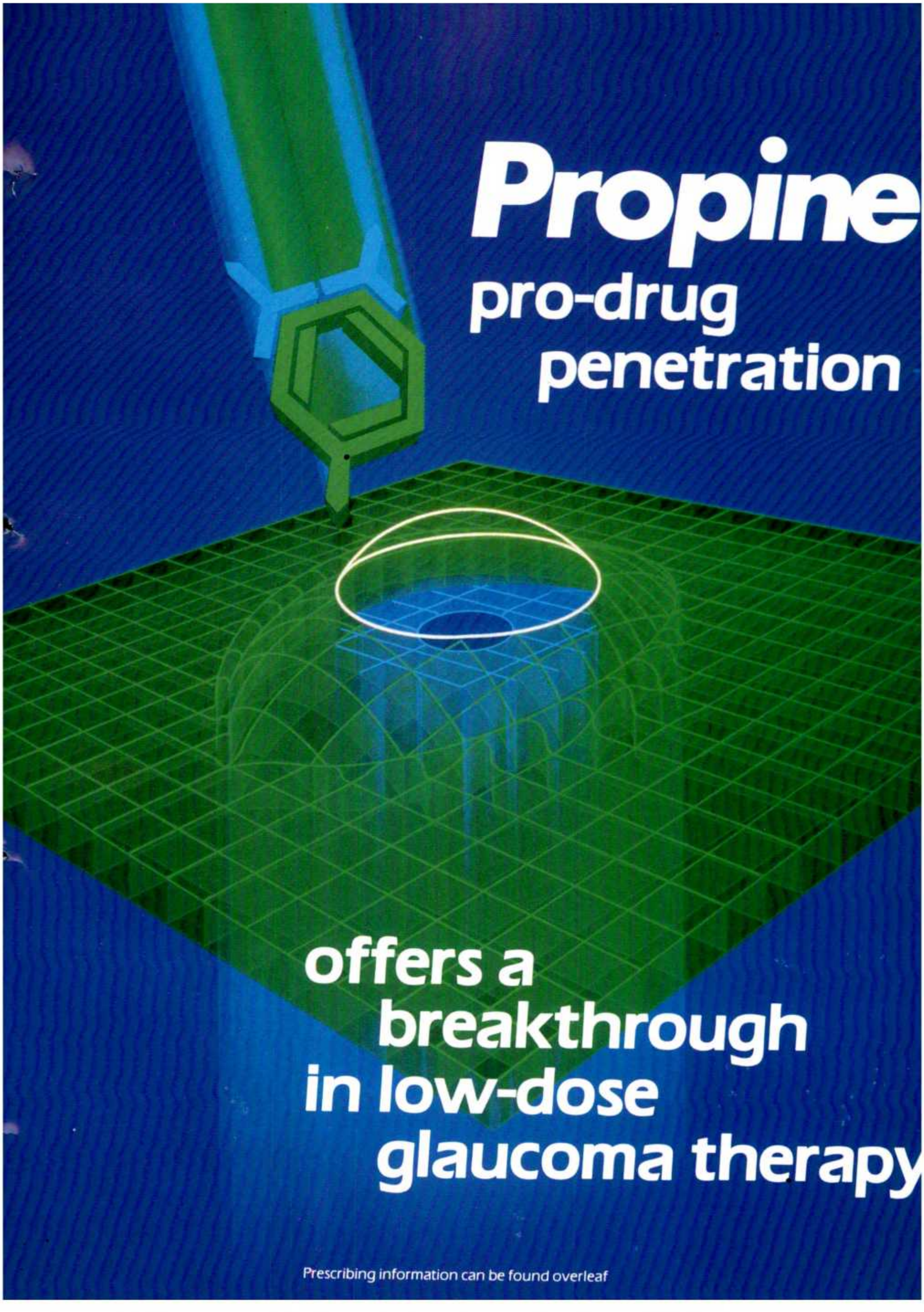
Blood was not seen behind the iridectomy, and there was no significant relationship between iridectomy and vitreous haemorrhage. This suggests that bleeding does not often occur from the iridectomy directly into the vitreous. The finding of only one secondary wound haemorrhage in the series suggests that this too is an uncommon cause of vitreous haemorrhage.

The observation of vitreous haemorrhage without operative hyphaema in 20 intracapsular and seven extracapsular cases requires further explanation. It is most unlikely that a secondary wound haemorrhage into a closed chamber would have been missed, since each patient underwent frequent slit-lamp examination. An alternative explanation is that bleeding occurred from the ciliary body or peripheral retinal vessels due to zonular traction. Larssen and Osterlin[4] have demonstrated that 10% of eyes have occasional retinal vessels closer to the ora than the normal arcade pattern, and that zonular traction during lens extraction produces traction on the peripheral retina. The finding that chymotrypsin used for intracapsular surgery is associated with a decreased incidence of vitreous haemorrhage supports the theory of Larssen and Osterlin that extravasation may occur from the anterior retinal vessels. Type 3 haemorrhages as shown in Fig. 1 may correspond to the expected morphological pattern resulting from localised extravasation into the vitreous base, while type 1 and type 2 haemorrhages correspond to the pattern expected as a result of blood traversing the hyaloid face or zonules from the anterior chamber. Extracapsular cataract extractions may well be accompanied by some zonular traction, especially during capsulotomy and perhaps also during expression of the nucleus. Saracco *et al.*[2] examined 150 aphakic eyes from one month to more than two years postoperatively with a three-mirror lens, and reported four types of retinal haemorrhage. 13·3% of cases had small haemorrhages observed near the ora, often in rows parallel to the limbus. Friedman *et al.*[3] reported a similar type of retinal haemorrhage in 10% of 200 aphakic eyes. Neither group reported vitreous haemorrhages.

We also observed retinal haemorrhages of this type, most common in the superior temporal quadrant; however, they were not included in the statistical analysis. Some of these retinal haemorrhages may also occur as a result of zonular traction.

The significance of vitreous haemorrhage in small amounts remains to be determined. Although we found no relationship with cystoid macular oedema or poor visual results in the short term, it may well be related to the vitreoretinal pathology of aphakia, and ultimately to the increased incidence of retinal detachment after intracapsular extraction.[6-10] Regnault[11] and others[12,13] have demonstrated that iron causes vitreous syneresis, with aggregation of vitreous fibrils and loss of hyaluronate. A threshold dose for significant syneresis is unknown, but the possible significance of subclinical haemorrhage is worth consideration. The consequences of extensive vitreous haemorrhage have been reviewed by Benson and Spalter.[12]

Extracapsular surgery is known to have a lower incidence of retinal detachment[4,7,9] than intracapsular surgery. Although the relative vitreous syneresis in the two groups remains uncertain, the presence of blood in the vitreous may be a contributory factor. Corneal section combined with routine extracapsular extraction is an effective method of minimising operative hyphaema and vitreous haemorrhage and according to the available data is the technique most likely to avoid vitreoretinal complications.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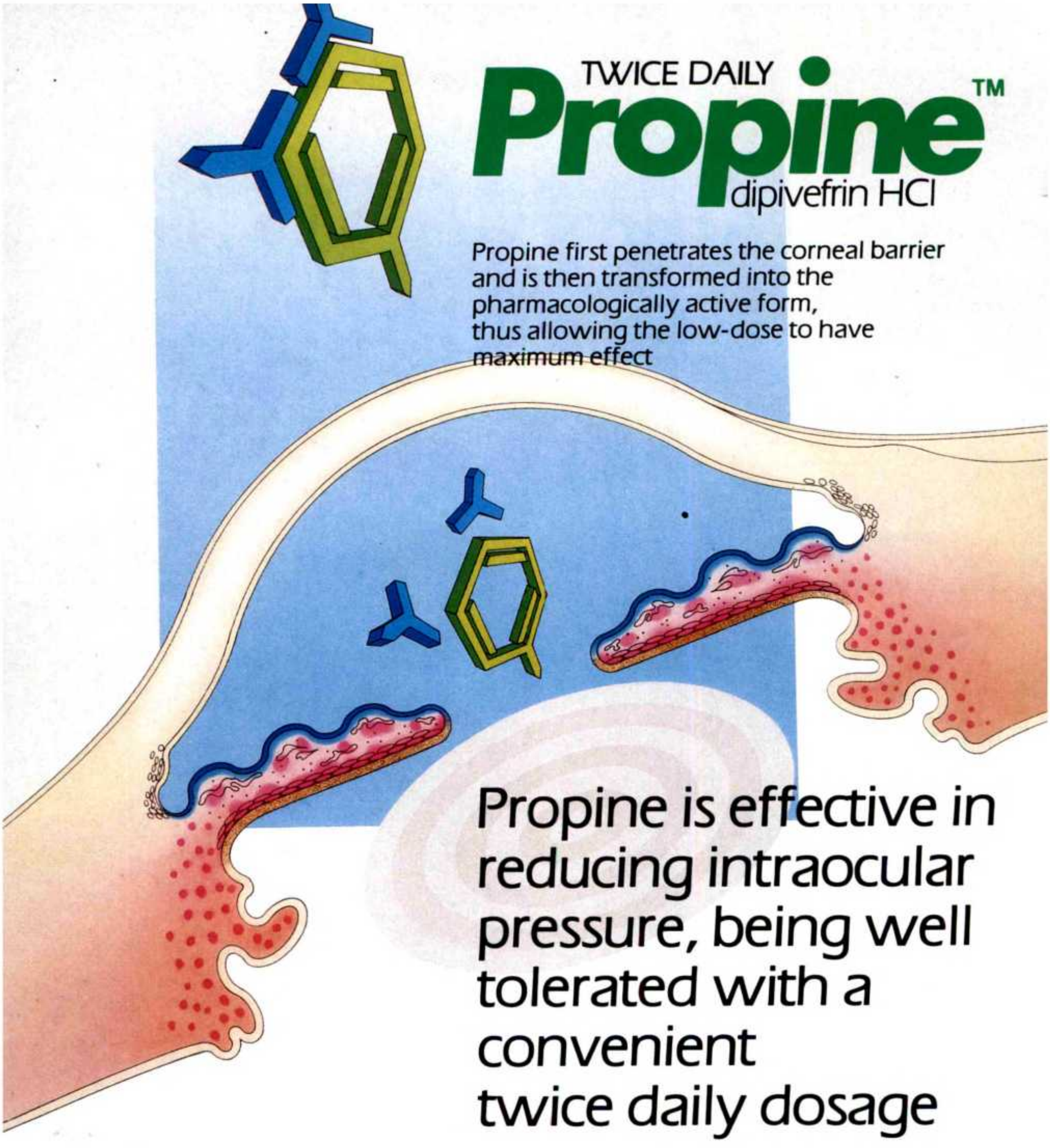

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A retrospective review of endophthalmitis due to coagulase-negative staphylococci

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SUMMARY We retrospectively reviewed 28 cases of postoperative endophthalmitis due to coagulase-negative staphylococci. There was an average delay between surgery and the acute presentation of 7·2 days (SD 3·3). All patients were treated with intraocular antibiotics (IOAB) or therapeutic vitrectomy with IOAB. In six of the 28 cases the organisms were resistant to gentamicin as measured by the Kirby-Bauer technique; none was resistant to cephalosporins. Isolates that had been stored by lyophilisation were reconstituted and tested by serial dilution; none was resistant to gentamicin, though two were borderline. The final visual acuity was 6/18 or better in 72% of the eyes.

In 1964 Theodore suggested that *Staphylococcus epidermidis* could be a causative organism in endophthalmitis.[1] Although *S. epidermidis* grew commonly about normal eyes, most physicians did not regard it as a pathogen. This was in spite of a report in 1898 by Gifford who described the abundance, persistence, and accessibility of this bacterium at the time of intraocular surgery.[2] In addition Gifford succeeded in recovering nearly 6/6 vision in a person with endophthalmitis following cataract extraction when he removed the purulent material and cultured *S epidermidis*. In the modern literature Valenton *et al.* first reported isolation of *S. epidermidis* in 1973 from the aqueous in two cases of endophthalmitis after cataract extraction.[3]

Controversy centres on choices in management.[4-10] Because the organism is of low virulence, administration of periocular antibiotics may be sufficient therapy. When this is true, invasive procedures such as an intraocular injection of antibiotics and vitrectomy may cause more damage than the disease. On the other hand such non-invasive therapy assumes that the aetiological diagnosis can be made without culturing intraocular fluids. We prefer to make the diagnosis based on cultures of the vitreous and aqueous. For eyes judged to have severe inflammation we perform a vitrectomy.

We here retrospectively review the clinical courses of 28 cases referred with endophthalmitis due to coagulase-negative staphylococci after intraocular surgery. We also review four cases of endophthalmitis due to traumatic perforation of the globe. We collected the preserved isolates of coagulase-negative staphylococci and measured their sensitivity to antibiotics.

Materials and methods

We reviewed all cases of endophthalmitis referred to the Bascom Palmer Eye Institute between 1973 and 1981. In 36 eyes coagulase-negative staphylococci were isolated from the intraocular fluids; however, only 32 records were available. There were 28 postsurgical and four post-traumatic patients. For six of the postsurgical cases we could not obtain the visual acuity six weeks after treatment. Therefore we here retrospectively review the 28 postsurgical cases and present clinical data on 22 cases.

Patients had both aqueous and vitreous samples collected and examined by techniques previously reported.[10-12] During the eight years that these patients were referred, sensitivities to antibiotics were routinely determined by the Kirby-Bauer agar-diffusion technique.[13] Twenty-six of the isolates were stored after lyophilisation. They were reconstituted, grown on blood agar, subcultured, and tested by serial dilution for minimum inhibitory concentrations of antibiotics with commercially available trays.[14]

Patients were managed by different faculty members at the Institute, and vitrectomies were performed by different surgeons. All patients were

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treated with intravenous and topical gentamicin and a cephalosporin.

Results

For the 28 postsurgical cases of endophthalmitis there was a predominance (18/28) of intracapsular cataract extractions (Table 1). This reflects the operation of choice during this period of 1973 to 1981. In the last year extracapsular surgery (5/28) became more popular. We cannot calculate the incidence of endophthalmitis or the relative risk of the operations, since the total number of operations of either type performed at the referring hospitals was not available.

The majority (18/27) of patients presented after their initial surgery with a best vision of hand motion. Fewer (5/27) had only light perception. Three had finger counting, and one was 6/21. Where recorded (17/21), there was marked pain, and the vision decreased dramatically over the 24 to 48 hours preceding diagnostic paracentesis. Although the clinical appearance immediately preceding diagnosis was typical for endophthalmitis, most cases had a quiescent or subacute period before becoming acute. Thus there was a delay between the initial surgery or a subsequent separation of the incision and the diagnosis of 7·2 days (SD 3·3), with a range of 2 to 15 days, for 27 postsurgical cases. One exceptional case had a latent period of 139 days. The incision remained intact, and he had no surgery until the diagnostic paracentesis. This long delay is so different from that of all the others that it may represent a separate mechanism of disease. It was therefore arbitrarily excluded from the calculations. For the post-trauma patients the time between the perforation of the eye and the diagnosis was 2·5 days (SD 1·9).

Sixteen patients received one or more prophylactic antibiotics either topically or subconjunctivally at the time of surgery as follows: gentamicin 12, neomycin 8, chloromycetin 6. There were four patients for whom there was no record of treatment with prophylactic antibiotics. For the remaining eight of the 28 postoperative patients the records were not sufficiently complete to determine their perioperative therapy. With these limited, retrospective data there is no significant difference in the delay of presentation between the 16 who received antibiotics (7·9 days, SD 3·8) and the four who did not receive treatment (6·2 days, SD 1·8).

There was no significant difference in the delay from surgery to the diagnosis by culture for those patients who received topical and/or subconjunctival steroids at surgery. For the 17 who received steroids, the quiescent period was 7·8 days (SD 3·8) with a range of 2 to 15 days. For the six who got no steroids the delay was 6·5 days (SD 2·5). There were no data for five patients.

All vitreous specimens that were cultured were positive by criteria previously described.[10-12] However, fewer than half of the concomitant aqueous specimens were positive (Table 2). In no cases did bacteria grow in the aqueous and not in the vitreous aliquots. Likewise a Gram stain of the vitreous was frequently (68%) positive, but the Gram stain of the aqueous was infrequently (17%) positive.

When patients presented, sensitivities for antibiotics were measured for isolates by the Kirby-Bauer technique (Table 3) Only against cephalosporin was there no resistance. Against gentamicin 21% (6/28) were resistant.

The 26 isolates that had been preserved by lyophilisation were tested for their sensitivity to six

Table 1 *Type of surgery leading to endophthalmitis*

Intracapsular cataract extraction	13
Extracapsular cataract extraction	0
Extracapsular cataract extraction with Intraocular Lens	5
Intracapsular cataract extraction with Intraocular Lens	5
Secondary intraocular lens	1
Trabeculectomy/vitrectomy	1
Penetrating keratoplasty	1
Suture removal	1
Radial keratotomy	1
Total	28

Table 2 *Results of Gram stain and cultures of intraocular fluids*

	Number examined	*Number positive*
Gram stain		
Aqueous	12	2 (17%)
Vitreous	19	13 (68%)
Cultures		
Aqueous	21	9 (43%)
Vitreous	32	32 (100%)

Table 3 *Sensitivities to antibiotics measured by Kirby-Bauer technique*

	Number sensitive/ number tested	*Sensitive (%)*
Cephalosporin	28/28	100
Vancomycin	26/27	96
Gantrisin	25/27	93
Bacitracin	24/27	89
Gentamicin	22/28	79
Erythromycin	22/28	79
Oxacillin	20/28	71
Methicillin	17/25	68
Neomycin	14/22	64
Kanamycin	14/25	56
Tetracycline	12/26	46

antibiotics by measuring minimum inhibitory concentrations (MIC). The majority were sensitive (Table 4). Although 79% (22/28) had been sensitive to gentamicin by Kirby-Bauer techniques, by serial dilution all 26 were sensitive to gentamicin with MICs of 4 μg/ml or less. We repeated measurements by Kirby-Bauer on the four available, preserved isolates initially found to be resistant to gentamicin. Two remained resistant, with zones of 7 mm and 8 mm; their MICs were both 4 μg/ml. One was borderline, with a zone of 14 mm; its MIC was 2 μg/ml. A fourth isolate was sensitive with a zone of 25 mm; its MIC was less than 0·5 μg/ml. (SI conversion: μg/ml=mg/l.)

Clinical data for 22 of the 28 postoperative patients appear in Table 5. Six were not included because final visual acuity was not available. The data show that the final vision was 6/18 or better in the majority

Table 4 *Distribution of the 26 isolates as a function of minimum inhibitory concentration for each antibiotics*

	Minimum inhibitory concentration (μg/ml)							
	0·25	*0·50*	*1*	*2*	*4*	*8*	*16*	*>16*
	Sensitive	Resistant						
Ampicillin	19		3	2	2			
Clindamicin	23						1	2
Methicillin	2	13	4	2	3	1	1	0
Erythromycin	21						1	4
Gentamicin		23		1	2			
Chloramphenicol		5	13	1		1	6	
						Sensitive	Resistant	

Table 5 *Visual outcome, quiescent periods, and therapy for endophthalmitis secondary to surgery for 22 patients with at least six weeks' follow-up*

Final vision	*Initial vision*	*Days from initial surgery to diagnosis*	*Days from symptoms to diagnosis*	*Intravitreal antibiotics*	*Resistance to antibiotics*	*Steroids*	*Vitrectomy*
6/6	20/80	4	1	G,Z		SC,GT	
6/6	HM(2')	10	2	G,L		SC,GT	+
6/6	CF	(52)* 3	2	G,L		SC	+
6/9	HM(3')	8	3	G,L		SC	
6/9	HM(2')	14	2		G	PO,GT	
6/12	HM(2')	10	1	G,L		GT	+
6/12	LPP	4	1	G,Z		SC,GT	+
6/12	HM	(54)† 8	6	G,Z		GT	+
6/12	HM(1')	8	2	G,Z		PO,GT	
6/12	HM(2')	6	1	G,Z		GT	
6/15	Bare HM	NA	NA	G,L		SC,GT	+
6/15	3/200	9	2	NA		NA	+
6/18	HM	6	1	G,L		SC	
6/18	HM(1')	4	1	G,Z	G	SC	
6/18	HM(1')	9	1	G,L		SC,GT	
6/18	HM	(15)‡ 3	1	G,L		SC,GT	+
LP	HM(1')	8	1	G,L		SC,GT	+
LP	HM(2')	5	2	G,L		PO	+
LP	CF(1')	139	123	G,Z	G	GT	+
LP	LPP	6	4	G,Z		GT	+
LP	HM(1')	9	1	G,L		SC	
Enucleated	Bare LP	4	2	G,Z		SC,GT	+

*Patient was doing well until 40 days after surgery, when he had an episode of vomiting. Vitreous wick was found and removed surgically on day 49.

†Patient was doing well until 46 days after surgery, when a suture was cut.

‡Patient was doing well until 12 days after surgery, when he slept without a shield; a gape in the wound was noted.

NA=not available. L=cephaloridine. Z=gentamicin and cefazolin. G=gentamicin. LP=light-perception. LPP=light-perception with projection. HM=hand motion at (feet). SC=subconjunctival dexamethazone. PO=oral prednisone. GT=drops of prednisolone acetate.

(16/22), yet only three presented with better than hand motion vision. The average delay in days between surgery and diagnosis for those with a final vision of 6/18 or better was 7·1 days (SD 3·2). Apart from the case with the unusually long delay, for those who attained a vision worse than 6/18 the delay was 6·4 days (SD 2·1).

At the time of diagnostic paracentesis steroids were given subconjunctivally (13/21), orally (3/21), and topically (15/21). No eye received intravitreal steroids. These data are insufficient to evaluate any correlation between their use and the visual outcome.

Most patients (13/22) had a therapeutic vitrectomy, and more than half (8/13) recovered 6/18 or better vision. A vitrectomy did not ensure a good final vision. In fact most (5/6) of those whose final vision was light perception or less had had a vitrectomy.

Discussion

The earliest reported case of recovery of 6/6 vision after culture-proved endophthalmitis with *S. epidermidis* was by Gifford in 1898.[3] He reasoned that the source must be the lids or conjunctiva. Therefore he examined various procedures in an attempt to sterilise the operative field. He concluded that it is impossible to eradicate the bacteria; the observation is true today. *S. epidermidis* is the bacterium most commonly found on the extracted lens[15] and is the commonest cause of postsurgical endophthalmitis.[9] Since the threat remains ever present, one must know its characteristics to be able to recognise and treat the infection effectively.

The rarity of endophthalmitis makes the prospective accumulation of cases for scientific investigation difficult. In addition it is hard to randomise treatment in this potentially devastating disease. Each ophthalmologist manages his patients in the way he considers best. We reason that we cannot identify the causative organism without culturing intraocular fluids. To await the results of the cultures for definitive diagnosis before instituting a therapy that has demonstrated effectiveness is to risk the demise of the eye.

A second judgment selects those with the severest inflammation. Because we suspect that they will have progressive damage to intraocular structures by inflammatory cells, or that they may not be sterilised completely by the injected antibiotics, or that they might have a more rapid recovery of vision, we perform a vitrectomy in selected cases based on the severity of the inflammation.[4 16] This treatment contrasts with the series reported by O'Day *et al.*[7] After obtaining intraocular fluids for culturing, they treated 18 consecutive postsurgical cases of endophthalmitis with *S. epidermidis* using combined antibiotic and corticosteroid therapy without intravitreal injection or vitrectomy. Of those, 78% achieved a final vision of 6/15 or better. In our 22 postoperative cases 55% achieved 6/15 or better and 72% obtained 6/18 or better. Of the 13 who also had a therapeutic vitrectomy 61% recovered 6/18 or better vision. This is similar to the results of Pauliafito *et al.*, who reported a final vision of 6/60 or better in three of five cases (60%) treated with both vitrectomy and intraocular antibiotics.[9]

The unusually long subacute phase is consistent with a low virulence and suggests that external factors can temporarily delay its toxic effects.[4] If this is true, one would expect a greater delay from surgery to diagnosis with the use of prophylactic antibiotics. When 16 patients received either topical or subconjunctival antibiotics peroperatively, the overall delay to diagnosis was 7·9 days. In four who received no antibiotics the quiescent period averaged 6·2 days. These delays are not statistically different. For the 17 patients who had steroids preoperatively the average subacute period was 7·8 days. The six who did not get steroids had an average quiescent period of only 6·5 days. The results in two groups are not statistically different.

At surgery there is a deliberate effort to cleanse the eyelids and conjunctiva. This contrasts with the treatment of trauma, where the tissues may harbour copious organisms. Likewise, one finds that the clinical courses for these two situations are different. After surgery the average duration of the quiescent period for all patients is 7·2 days and the final vision was better than 6/18 in 72%. After trauma the quiescent period averaged 2·5 days and all patients had 6/120 or less final visual acuity. These differences are likely related both to the intraocular trauma and to the quantity of bacteria inoculated into the eye.

For the diagnosis of endophthalmitis Forster has recommended culturing the vitreous.[8] Previously he found that 36% of samples of intraocular fluids showed no growth from the aqueous when organisms grew out of the vitreous. In this series of endophthalmitis due to coagulase-negative staphylococci 57% had no growth from the aqueous when the vitreous was positive. In addition the Gram stain of the vitreous demonstrated bacteria four times more often than the aqueous. Sampling the aqueous in suspected endophthalmitis is insufficient; it is important to obtain a vitreous sample.

There was a 21% (6/28) resistance to gentamicin as measured by Kirby-Bauer technique (Table 3). However, when the four available isolates were retested by serial dilution, none was resistant (Table 4). All patients also received a cephalosporin intraocularly, and no coagulase-negative staphylococci were resistant to a cephalosporin by the Kirby-Bauer technique or serial dilution. Pauliafito *et al.* found that 37% of isolates were resistant by the Kirby-Bauer technique.[9] They did not measure the MIC. For bacitracin, methicillin, and erythromycin they measured percentages of resistant isolates as 16%, 32%, and 37%. This compares with 11%, 32%, and 21% respectively reported here. Multiply resistant coagulase-negative staphylococci can come from the lids, and not all are sensitive to cephalosporins.[17] Since the lids and conjunctiva may be a source of endophthalmitis, they should be cultured when endophthalmitis is suspected.

The resistance observed for these coagulase-negative staphylococci emphasises a need for determining species in isolates. Since subtyping is not normally done in most laboratories and hospitals, most organisms are reported as *S. epidermidis*. Resistance in *S. epidermidis* may be a manifestation of diversity in coagulase-negative staphylococci. In like fashion this lack of subtyping may explain variability in virulence. Here one relatively non-virulent bacterium had a subacute phase of 139 days. It was arbitrarily excluded from the calculation of the average quiescent period because it was unique. None of these coagulase-negative staphylococci were subtyped.

Because this is a retrospective study, conclusions drawn from the data are not without bias. In addition these are disparate cases treated by multiple physicians employing surgical judgment, and the records are not complete. In spite of these deficiencies this review suggests the following. With endophthalmitis due to coagulase-negative endophthalmitis there may be a subacute period of a week before diagnosis. In trauma the delay may be less than half as long. Cultures of the vitreous are more often positive than those of the aqueous. We recommend culturing both. Antibiotic therapy with intravitreal injection and selected vitrectomy gives results similar to antibiotic therapy with no intraocular injection. Resistance to gentamicin occurs when sensitivity is measured by the Kirby-Bauer technique and not by serial dilution. Because of the possible resistance a cephalosporin is indicated.

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Corneal ulceration at an urban African hospital

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SUMMARY During a one-year survey 283 corneal ulcers from 274 patients were seen at St John's Eye Unit of Baragwanath Hospital. Central bacterial ulcers constituted the largest problem, and the commonest isolate in this group was *Streptococcus pneumoniae*. Mycotic and dendritic keratitis were relatively uncommon, while marginal catarrhal ulceration secondary to chronic staphylococcal lid disease was frequently seen. The microbiology of the various ulcers is described, and the placing of organisms into classes is stressed in determining significance of isolates. Many of the patients were male Africans who were either manual labourers or unemployed. Half the patients had used topical antibiotics before presentation.

The spectrum of micro-organisms responsible for corneal ulceration varies according to geographical location. Reports from the northern parts of the United States of America show predominantly Gram-positive organisms[1 2] while the southern parts show a striking number of fungal and Gram-negative isolates.[3] A recent study from Britain[4] also showed predominantly Gram-positive isolates. Variations such as these are probably worldwide, but studies of them have not been forthcoming from many areas. Relatively little is known about the situation in Africa. A report from Nigeria in 1976[5] concentrated on cases of mycotic keratitis selected from the 'large number of patients with corneal ulcers' treated at that hospital.

Baragwanath Hospital serves the population of Soweto, a sprawling city near Johannesburg, South Africa, whose inhabitants number about one million. In addition Baragwanath Hospital is a referral centre for medical problems from many parts of the country and occasionally further afield. The St John's Eye Unit is an integral part of the hospital and is adjacent to it. Cases of corneal ulceration constitute about 5% of admissions to St John's Eye Unit. The present survey was intended to establish the numbers of the various types of corneal ulcers seen at the hospital, the spectrum of micro-organisms isolated, and to collect data relating to local and general predisposing factors with a view to prophylactic intervention should this be possible.

Material and methods

PATIENTS

Patients with corneal ulcers were divided into mild, moderate, and severe groups. The mild group contained patients with corneal ulcers considered suitable for outpatient treatment. Patients with moderate and severe corneal ulcers were admitted for intensive investigation and treatment. The severe cases had features of severity as defined by Jones.[6] Ulceration due to chemical burns and simple traumatic ulcers without secondary infection were excluded from the study group.

From the beginning of July 1982 to the end of June 1983 113 cases of mild corneal ulceration (116 eyes) and 161 moderate and severe cases (167 eyes) were treated. The mild group was treated in the outpatient department by a number of different doctors, and treatment methods varied.

Recording sheets were used to detail relevant history and examination, and a drawing of the cornea was made along the lines suggested by Bron[7] and Harrison.[8] Anterior segment photography recorded the appearance of the ulcer on admission, discharge, and when otherwise indicated.

CULTURE TECHNIQUES

All cultures except two were taken prior to admission by the doctor supervising the cases, and the other two were cultured under direct supervision by the same technique.

The culture technique was as advocated by Jones.[9] Conjunctival specimens were taken with calcium alginate swabs (Calgiswab, Inolex) moistened in

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Correspondence to Dr T R Carmichael, Department of Ophthalmology, Medical School, York Road, Parktown, Johannesburg 2193 South Africa serum broth. One was swabbed over the lower fornix, avoiding the lid margins, plated on to blood agar, and inoculated into serum broth. A second swab was moistened in chopped meat broth and a conjunctival swab taken in the same way and placed in the chopped meat broth. The cornea was then anaesthetised with oxybuprocaine or proparacaine hydrochloride. Multiple corneal scrapings were then taken with platinum spatulae and inoculated on to blood agar in several rows, and serum broth and brain-heart infusion broth were also inoculated. From corneal scrapings two smears were made, one of which was stained the same day with Gram's staining technique, while the other was examined microscopically the following day by the Mycology Department. A swab moistened in chopped meat broth was rubbed over the base and edges of the ulcer and inserted into the chopped meat broth. The chopped meat broth replaced a brain-heart infusion broth under oil which was used for the first four months of the study (80 cases) and during which time no anaerobic bacteria were grown. In 54 cases a dry cotton swab was used to take a specimen for viral culture, and this was placed in bovine plasma albumin for transport to the laboratory. In 30 cases corneal scrapings were plated on to Lowenstein and Jensen media to check specifically for mycobacteria, as tuberculosis is not uncommonly treated at Baragwanath Hospital. The viral cultures were kept at 4°C and the rest of the specimens were incubated overnight. The serum broths were incubated in 10% CO_2 to enhance the growth of more fastidious organisms. Swabs moistened in serum broth were used to take lid margin cultures from the same eye in cases of marginal corneal ulcer, and these were plated on to blood agar.

Bacteria were classified according to Bergey's *Manual.*[illegible] Conventional microbiological techniques were used for the isolation and identification of bacteria, fungi, and viruses isolated. All specimens were processed by the Central SAIMR (South African Institute for Medical Research), Johannesburg, except for virology specimens, which were forwarded to the National Institute for Virology.

CLASSIFICATION OF ISOLATES

The following classification to determine the significance of bacterial isolates, suggested by Jones,[4] was used:

Class 1. Growth of any organism(s) in two or more corneal media.

Class 2. Growth (more than one colony) in one solid medium of *Staphylococcus aureus*, *Streptococcus pneumoniae*, or *Pseudomonas aeruginosa*.

Class 3. Growth in one medium of an organism identified in the direct smear.

In addition to these three classes it was found useful to consider two other situations for clinical purposes, though these may not be acceptable in terms of a case definition:

Class 4. Growth of any organism(s) in a corneal medium plus conjunctival media.

Class 5. Growth of a pathogen on conjunctival media only.

As anaerobic bacteria were cultured from a single corneal and conjunctival medium these were not placed in the above mentioned classes.

A simple classification of the ulcers was used according to a method similar to that described by Kumura.[11]

Results

The number of ulcers in each category is shown in Table 1. There was a slight seasonal variance in the presentation of the ulcers to the hospital with a peak late in winter and into spring. There were 79 right and 76 left eyes with unilateral ulcers, and these together with the six bilateral cases gave 161 patients with 167 ulcers. Three of the bilateral cases were marginal catarrhal. There was no significant difference in mean age between the two largest groups. The central bacterial group had a mean age of 42·5 years and the marginal catarrhal group a mean age of 44·9 years. Within the group of admitted patients 30

Table 1 *Types of corneal ulcers*

Type of ulcer	*Number of eyes*	
	Mild (outpatients)	*Moderate and severe (admitted cases)*
Central.		
Bacterial	30	91
Fungal	0	6
Viral	24	13
Other	0	0
Marginal.		
Catarrhal	30	30
Ring/melting	4	12
Mooren's	0	4
Primary infection	0	6
Other	28	5
Total	116	167

Table 2 *Occupation of adult corneal ulcer patients*

Type of work	*Number*	*Percentage*
Manual labourer (non-farm)	61	47
Manual labourer (farm)	8	6
Unemployed	33	25
Domestic worker	16	12
Pensioner	11	8
Clerical	2	2
Total	131	100

Table 3 *Comparison of numbers of central bacterial and marginal catarrhal corneal ulcers in the various ethnic groups*

Ethnic group	*Central bacterial*	*Marginal catarrhal*
Zulu	26	11
Sotho	22	9
Xhosa	8	4
Tswana	7	2
Ndebele	6	1
Swazi	6	1
Shangaan	5	0
Coloured	3	0
Venda	1	0
Indian	1	0
Not known/other	6	2
Total	91	30

Table 4 *Comparison of numbers of central bacterial and marginal catarrhal corneal ulcers for males and females*

Sex	*Central bacterial*	*Marginal catarrhal*
Male	79	21
Female	12	9
Total	91	30

ulcers occurred in children (16 years of age and younger). Of the adults half were manual labourers and a quarter were unemployed (Table 2).

Of the cases which were admitted to hospital, 39% originated from Soweto, 48% from other urban areas within the Transvaal province, and 13% from rural areas within the Transvaal Province. Tables 3 and 4 show the ethnic and sex distribution of patients with corneal ulcers in the two largest ulcer groups.

In 154 cases the mean delay between the onset of symptoms and presentation to St John's for treatment was 16 days, but there was marked variation depending on the type of ulcer (Table 5). There was a significantly longer ($p<0\cdot05$, Student's *t* test) delay before referral for the marginal catarrhal group than with the central bacterial group. About half the patients had been previously treated with topical antibiotics, and the antibiotic varied according to the type of ulcer being treated (Table 6). In 11 cases oral antibiotics had certainly been given in addition to local treatment. In a further five cases the description of the tablets suggested that they were antibiotics. Only one patient was on systemic steroid therapy, and this was a case of systemic lupus erythematosus with keratitis sicca which developed a pseudomonas corneal ulcer.

MICROBIOLOGY OF CENTRAL CORNEAL ULCERS

Corneal isolates were obtained in 62 of the 91 eyes in the central bacterial group (Table 7). By far the commonest isolate was *Str. pneumoniae*, which was cultured from 26 eyes. Other streptococcus species were isolated from a further four eyes. Of the pneumococci which were isolated from the central

Table 5 *Delay before presentation for treatment*

Type of ulcer	*Mean (days)*	*Number in group*
Central.		
Bacterial	11	82
Fungal	26	6
Viral	10	13
Marginal		
Catarrhal	19	29
Ring	34	12
Mooren's	43	3
Primary infection	27	5
Other	9	4
Total		154

Table 6 *Local treatment of corneal ulcers before admission*

Central group (110 ulcers)

	Bacterial	*Fungal*	*Viral*	*Total*	
Antibiotic:					
Definite	16	3	2	21	51
Probable	22	0	5	27	(46% of
plus Steroid	2	0	1	3	central ulcers)
Steroid only	3	0	1	4	
Antiviral	0	1	0	1	
Other	19	0	2	21	
Total	62	4	11	77 (70% of central ulcers)	

Marginal Group (57 ulcers)

	Catarrhal	*Ring*	*Mooren's*	*Primary infect.*	*Other*	*Total*	
Antibiotic:							
Definite	7	4	1	3	1	16	31
Probable	8	2	1	0	1	12	(54% of
plus Steroid	1	1	0	0	1	3	marginal ulcers)
Other	4	2	0	0	1	7	
Total	20	9	2	3	4	38 (67% of marginal ulcers)	

Antibiotic 'Definite'—the patient could produce the antibiotic or knew the name, 'probable'—the patient was using ointment, or drops and ointment, which had been obtained from a medical source such as a doctor, clinic or chemist, 'other'—the patient was using drops only, which may or may not have contained antibiotic.

bacterial ulcers four were isolated from children, three of whom were under 5 years old. From all types of ulcers there were 29 pneumococcal isolates, of which 24 were typed. Type 6 was the commonest (six isolates), followed by type 10 (four isolates). These and the eight other types reflected the usual upper respiratory tract pneumococci in the area. Minimal inhibitory concentrations (MICs) of drugs against 12 pneumococcal isolates were determined and they were all susceptible to penicillin-G MIC levels at <0·01 μg/ml except one which had an MIC of 0·25 μg/ml.

Staph. aureus was not found to be a common cause of central corneal ulceration in this survey. Isolates of Gram-negative bacteria were obtained from 18 eyes, with *Pseudomonas aeruginosa* (nine isolates) being the most common, followed by *Moraxella* species (four significant isolates).

In class 5 (conjunctival pathogens) there were three isolates of *Staph. aureus*, two of *Proteus mirabilis*, and one each of *Ps. aeruginosa* and *Str. pneumoniae*.

The anaerobes cultured were all obtained from chopped meat broth and consisted of nine isolates from eight cases. Four were conjunctival isolates only, and, of the remaining five, two were isolated in conjunction with class 1 pneumococci and were not considered significant in their own right. The remaining three were possibly significant. The case shown in Table 7 suffered from severe bullous keratopathy, and there were no aerobic bacteria cultured from the ulcer. The *Peptococcus prevotii* was cultured from the cornea and a *Peptococcus asaccharolyticus* was isolated from the conjunctiva. Scanty Gram-positive cocci were seen on the direct smear from the cornea. The other two isolates, a *Peptococcus micros* and a *Propionibacterium acnes* were not confirmed on direct smear and are thus probably not significant.

The Lowenstein-Jensen media were all negative for mycobacteria. The isolates from the cases of fungal keratitis are listed in Table 8 together with some of their relevant clinical details. None of the cases gave a history of trauma and none was wearing a contact lens. The nodular form of climatic droplet keratopathy which flakes off, leaving an area denuded of epithelium, was seen in two of these cases (it was also a local predisposing factor in eight of the central bacterial ulcers). As might be expected, half the group came from rural areas. There was only one significant bacterial isolate in this group and that was a class 1 *Staph. epidermidis* from case 5.

The group of central viral ulcers consisted largely of cases of indolent corneal ulceration with loss of corneal sensation. In some cases a clinical diagnosis could be made of stromal herpes keratitis with ulceration, and in one of these cases *Herpes simplex* was isolated. There was only one dendritic ulcer in this group.

Table 7 *Corneal isolates from central bacterial ulcers*

	Organism	*Number of isolates*
Single isolates		
Class 1	*Streptococcus pneumoniae*	20
	Pseudomonas aeruginosa	9
	Staphylococcus aureus	3
	Corynebacterium species	2
	Staph epidermidis	2
	Str sanguis	2
	Proteus mirabilis	2
	Moraxella lacunata	1
	Klebsiella pneumoniae	1
Class 2·	*Str pneumoniae*	1
Class 3.	*Moraxella lacunata*	3
	Str pneumoniae	1
	Corynebacterium species	1
Class 4:	*Staph epidermidis*	2
	Corynebacterium species	1
	Moraxella species	1
Anaerobe·	*Peptococcus prevotii*	1
Total		53 isolates from 53 eyes
Mixed isolates (class of isolates in brackets)*		
Str pneumoniae (2) + *Staph. aureus* (1)		
Str pneumoniae (2) + *Staph epidermidis* (4)		
Str. pneumoniae (1) + *Propionibacterium acnes*		
Str pneumoniae (1) + *Pasteurella* species (4)		
M lacunata (3) + *Corynebacterium* species (1)		
M lacunata (1) + *Staph. epidermidis* (1)		
Staph. epidermidis (4) + *Corynebacterium* species (4)		
Str pyogenes (1) + *Staph epidermidis* (1): this combination was isolated from both eyes of a case of bilateral corneal ulceration		
Total		18 isolates from 9 eyes

*For description of classes of isolates see 'Materials and methods'

Table 8 *Corneal isolates from central fungal ulcers*

Isolate	*Class of isolate*	*Rural*	*Predisposing factor*
Aspergillus flavus	1	Yes	Diabetic
*Phoma eupyrena**	1†	No	Climatic droplet
Candida guilliermondii	BHI	No	Diabetic
*Fusarium moniliforme**	1†	Yes	Nil
*Curvularia lunata**	BHI	No	Diabetic, renal
*Curvularia lunata**	1†	Yes	Climatic droplet

*Identification confirmed at the Identification Services, Commonwealth Mycological Institute, Surrey, England
†Confirmation of fungus on direct smear
BHI = Fungus cultured from brain heart infusion broth only after repeated corneal scraping in clinically suggestive cases
Climatic droplet means climatic droplet keratopathy.

MICROBIOLOGY OF MARGINAL CORNEAL ULCERS

The organisms isolated from the marginal catarrhal group are shown in Table 9.

Direct smears were helpful in 85 of the 128 instances (66%), in which one was done (see Table 10).

Table 9 *Corneal isolates from marginal catarrhal ulcers*

Organism	*Number of isolates*	*Class of isolate**
Single isolates		
Staphylococcus aureus	6	1, 1, 1, 3, 4, 4
Corynebacterium species	3	1, 4, 4
Staph. epidermidis	2	1, 4
Corynebacterium hofmanii	1	4
Streptococcus pneumoniae	1	1
Propionibacterium acnes	1	
Total	14 isolates from 14 eyes	
Mixed isolates (classes in brackets)		
Proteus mirabilis (4), *Str. pneumoniae* (4)		
Staph. aureus (1), *Str. pyogenes* (1)		
Staph. aureus (1), *Str. pyogenes* (1)		
Str. anginosus (1), *Neisseria flava* (4)		
Str. anginosus (1), *N. flava* (1), *Proteus vulgaris* (1)		
Total		11 isolates from 5 eyes (the last 2 eyes were from a bilateral case)

*For description of classes of isolates see 'Material and methods'.

Table 10 *Results of microscopy of smears*

Result	*Ulcer group (numbers)*		*Total*	
	Central	*Marginal*	*Number*	*Percentage*
Organism identified	40	7	47 } 85	37 } 66
Slide negative, Culture negative	23	15	38 }	29 }
Slide negative, Culture positive	21	20	41	32
Slide positive, Culture negative	2	0	2	2
Total	86	42	128	100

A hypopyon was present in 69 eyes, two-thirds of these being central bacterial ulcers. More than 80% of the hypopyons were 2 mm or less at the time of presentation. A significant corneal isolate was obtained in 45 of the 69 eyes, 17 of which were pneumococci. Ten of the 30 ulcers in the marginal catarrhal group were associated with hypopyon.

All aerobic bacterial isolations were tested for antibiotic susceptibility with a modified Kirby-Bauer disc diffusion technique on blood agar plates. All isolates were sensitive to either cefazolin or gentamicin, which were the two antibiotics used in treating the bacterial infections.

Discussion

Patients with many different types of corneal ulcers present for treatment at St John's Eye Hospital every year. As a general rule, owing to a shortage of beds (110 beds), only fairly severe cases will receive inpatient treatment, and this group of patients included 69 with hypopyon and 34 with perforated corneal ulcer. Most of the patients were male Africans, half of whom were manual labourers. This group might be expected to be exposed to corneal trauma, and indeed corneal foreign bodies and other corneal injuries such as corneal abrasions were the commonest local predisposing factors, followed by nodular climatic droplet keratopathy. The differences in the numbers of patients from various ethnic groups probably reflect differences in population size. The marked male predominance has commonly been reported and was as high as 80% in a retrospective study of 677 cases.[2]

The class system for the isolates is intended to assess relevance of isolates and exclude contaminant bacteria. From class 1 to class 5 presents a decreasing likelihood of significance. Florid growth of an organism in several media (class 1) would be highly significant, whereas recovery of a pathogen only from the conjunctiva would be of questionable significance. The latter isolate may be considered when pretreatment is suspected of having sterilised the cornea. Classes 4 and 5 are included in an attempt to use conjunctival isolates in a meaningful way rather than relying only on corneal specimens. A class 4 isolate may reflect a tear film contaminant such as *Staph. epidermidis* or a more fastidious organism that will grow only on a certain type of medium, such as *Moraxella* species in serum broth of cornea and conjunctiva. Conjunctival isolates obtained which did not occur as class 4 or 5 isolates are not reported in this paper.

Bacterial corneal ulcers constituted the largest group of ulcers seen, and pneumococci were prominently isolated within the group. *Staph. aureus* is usually the commonest Gram-positive bacterium reported as a cause of central bacterial keratitis,[1-4,6] though an early series reported by Thygeson[12] showed pneumococci to be causative in 70% of 50 central corneal ulcers. The difference in the range of organisms is at least partly due to a worldwide difference in the conjunctival sac carrier rates of various organisms.[1] In a large series Locatcher-Khorazo and Seegal[1] showed a high (13%) carrier rate of pneumococci in the normal conjunctival sac in the children under 5 but only 2–3% thereafter. In the same series the carrier rate of *Staph. aureus* was 25% in the children under 5, but this remained constant in all age groups thereafter. In this study five children had pneumococcal ulcers, four of whom were under 5 years old (three were central bacterial ulcers). The other pneumococcal ulcers were evenly spread through the age groups over 20 years.

Pneumococcal typing is not particularly useful in that the organisms usually reflect upper respiratory tract pneumococci.[1] This was found to be true in this study, though the types of pneumococci predominantly found differed from those previously reported. As multiply resistant pneumococci have been reported from South Africa,[13 14] a careful watch was kept for these organisms, but none was found. *Ps. aeruginosa* and *Moraxella* species were the two commonest Gram-negative isolates in the population studied. Moraxella corneal ulcers have been described as occurring in derelict populations, who have a high carrier rate of these organisms in their noses and conjunctival sacs.[15] The carrier rate in our area is not known.

Direct smears were found to be significantly more helpful in central as opposed to marginal ulcers ($p<0.05$, normal deviate test). This difference was largely due to the fact that an organism could be identified from many of the central ulcers. The results confirm the fact that, if an organism is seen on the smear, it is very likely to be the causative organism, but if no organism is seen there is still a 50% chance that an organism will be cultured.

Only 24 cases of dendritic keratitis were seen during the year (two admitted and 22 treated at outpatients). This might represent a racial difference in susceptibility, and in support of this seven of the 24 were coloured and one Asian. This was the only group of ulcers with such a large proportion of race groups other than African. There are many clinics throughout Soweto and the surrounding areas, and certainly many corneal ulcers are prevented or treated at an early stage by these primary health care workers. To some extent, therefore, the patients presenting to St John's for treatment represented a 'screened' population, but many 'mild' cases were seen, as well as referral problem cases, and it is unlikely that the dendritic ulcer patients were being selectively screened out.

The 60 catarrhal corneal ulcers treated during the year (half at outpatients and half admitted) testify that chronic staphylococcal blepharitis/meibomianitis and its sequelae were commonly seen, often with a secondary bacterial infection.

When dealing with large numbers of corneal ulcers the culture technique used must be accurate and yet reasonably quick to perform. The multiple scrape technique, described by Jones,[9] was largely successful in view of the fact that half the cases had been pretreated with antibiotics. The use of multiple media is essential if significance is to be determined and contaminants recognised. The serum broth was supplied in Bijou bottles and the brain-heart infusion and chopped meat in McCartney bottles, which made transport easier than with media in tubes.

Reliable isolation of anaerobic bacteria is more time-consuming than of aerobic bacteria, and indications are that these organisms should not be ignored. Corneal ulceration caused by anaerobic bacteria was considered uncommon enough to warrant single case reporting from the 1950s into the 1970s.[16–19] In 1977 Jones and Robinson reviewed the subject[20] and included details of five cases of anaerobic keratitis. They also proposed guide lines for defining a significant isolate. Perry *et al.*[21] reported 11 cases of anaerobic corneal ulcer, using very stringent criteria for case definition, from a series of 162 bacterial corneal ulcers. All these cases[20 21] had some predisposing factor(s). Anaerobic bacteria may be pathogenic alone or acting synergistically with aerobic bacteria as has been suggested.[22 23] The practical implications of this group of organisms with respect to treatment is uncertain, as they are usually susceptible to the same antibiotics as have been used for aerobic bacterial keratitis. A change to chloramphenicol is recommended[21] once an anaerobe is isolated, but this information may not be available in time to be useful.

If bacteriology is to play an active role in the management of acute keratitis, provisional results must be available within 24 hours, as these cases can deteriorate rapidly. It was pleasing to note during the study period that in nine cases of uncontrolled infection (six pneumonococcal and three pseudomonas) the organism was identified in eight cases on the day of admission on direct smear and provisionally confirmed on culture the following day. This places the clinician in the best possible position to make decisions on antibiotic choices in spite of having to wait a further day for antibiotic sensitivity results. It is usually sufficient to be able to make a distinction between Gram-positive cocci and Gram-negative bacilli for the purpose of choosing an antibiotic. Mixed infections are common enough to keep one humble, and a broad spectrum of antibiotic cover is used initially, with a change to more specific treatment made with positive confirmation of the causative organism.

Dr L D Ormerod suggested the study and Dr E T Meyer's assistance is gratefully acknowledged. The laboratory personnel provided useful comments, and suggestions and the registrars and nursing staff at St John's Eye Hospital made the study possible.

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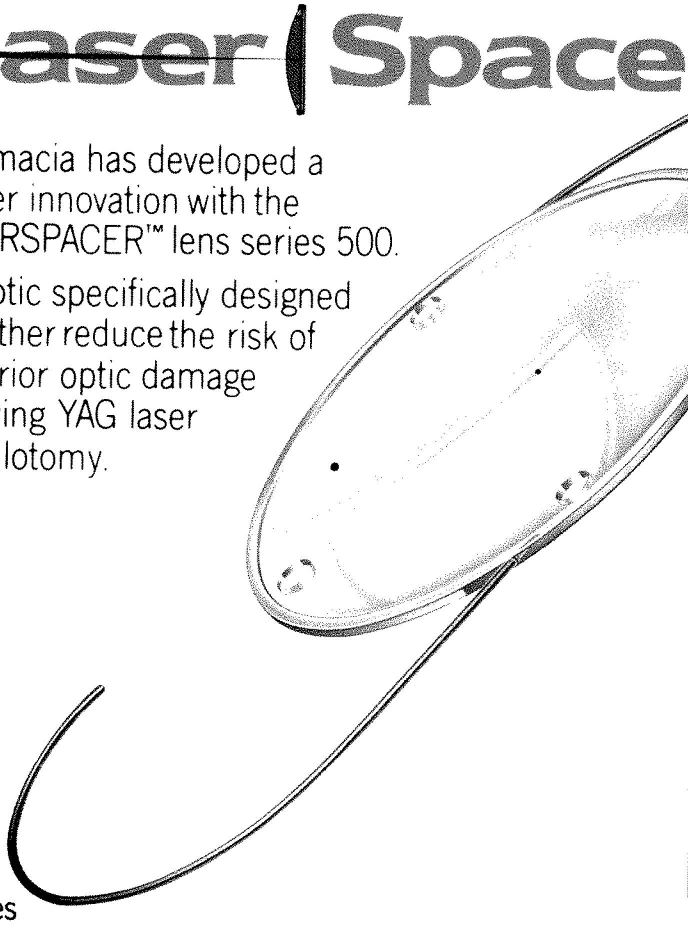

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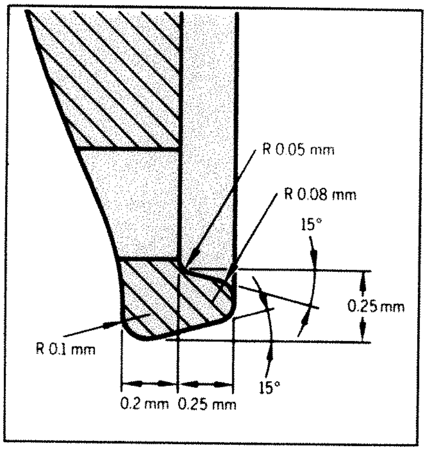

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Oculokinetic perimetry: a simple visual field test for use in the community

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SUMMARY A method of visual field examination is described which enables an unsupervised person to carry out self-assessment using only a paper test chart, a record sheet, and a pencil. It is entitled 'oculokinetic perimetry' because it is the subject's eye that moves and not the test target. By providing non-ophthalmic health care workers with a simple means of performing perimetry in the community, and by allowing susceptible people to carry out self-assessment of the visual fields at home, this test should facilitate the detection and management of glaucoma, especially in underdeveloped countries.

Visual field examination has an invaluable role in the diagnosis and management of glaucoma and other important ocular and neurological disorders.[1] For this reason remarkable technological advances have recently taken place in perimetry[2] in order to improve results. However, these developments have done little to facilitate the detection and monitoring of visual field defects outside ophthalmic clinics. At present examination of the visual fields to confrontation remains the sole means available to many physicians, and with few exceptions[3] self-assessment of the visual fields at home is of benefit only to patients who have paracentral visual defects.[4] These limitations occur because conventional methods of perimetry (whereby one or more test stimuli are introduced into the peripheral visual field of an immobile eye) require a highly trained observer and/or expensive equipment (*a*) to move the test target through all areas of the visual field, (*b*) to ensure that the subject's eye remains immobile throughout the examination, and (*c*) to plot the results. The author has attempted to overcome these three obstacles to more universal perimetry by developing an alternative method of visual field examination which is entitled 'oculokinetic perimetry' because it is the subject's eye that is moved and not the test stimulus.

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Material and methods

OCULOKINETIC VISUAL FIELD TEST

The test chart consists of a white sheet of paper with 100 numbers distributed around a central test stimulus in such a manner as to increase the chances of detecting arcuate, quadrantic, hemianopic, and altitudinal visual field defects as well as a nasal step (Fig. 1).

The numbers are printed in an unsaturated blue colour to avoid confusion with the test stimulus, which is coloured black so that it can if necessary be easily enlarged with an ordinary pen or pencil. The size of the test stimulus (1·4/333·3 mm) subtends a visual angle of 0·25°, so that it is barely visible to normal persons at 25° from fixation. The record sheet comprises two small versions of the test chart with a set of instructions on the reverse side.

The test is carried out with the test chart attached to a well-lit vertical surface, its centre being placed at eye level. The right eye is tested first so that, soon after starting the examination, the subject is reassured by the detection of the blind spot that the correct procedure is being followed. The correct working distance is found by looking down at the star near the lower border of the chart, covering one eye, and moving backwards or forwards until the letter L or R (for the left and right eye respectively) is no longer visible. The numbers are then read slowly from 1 to 100 so that the test target moves through all

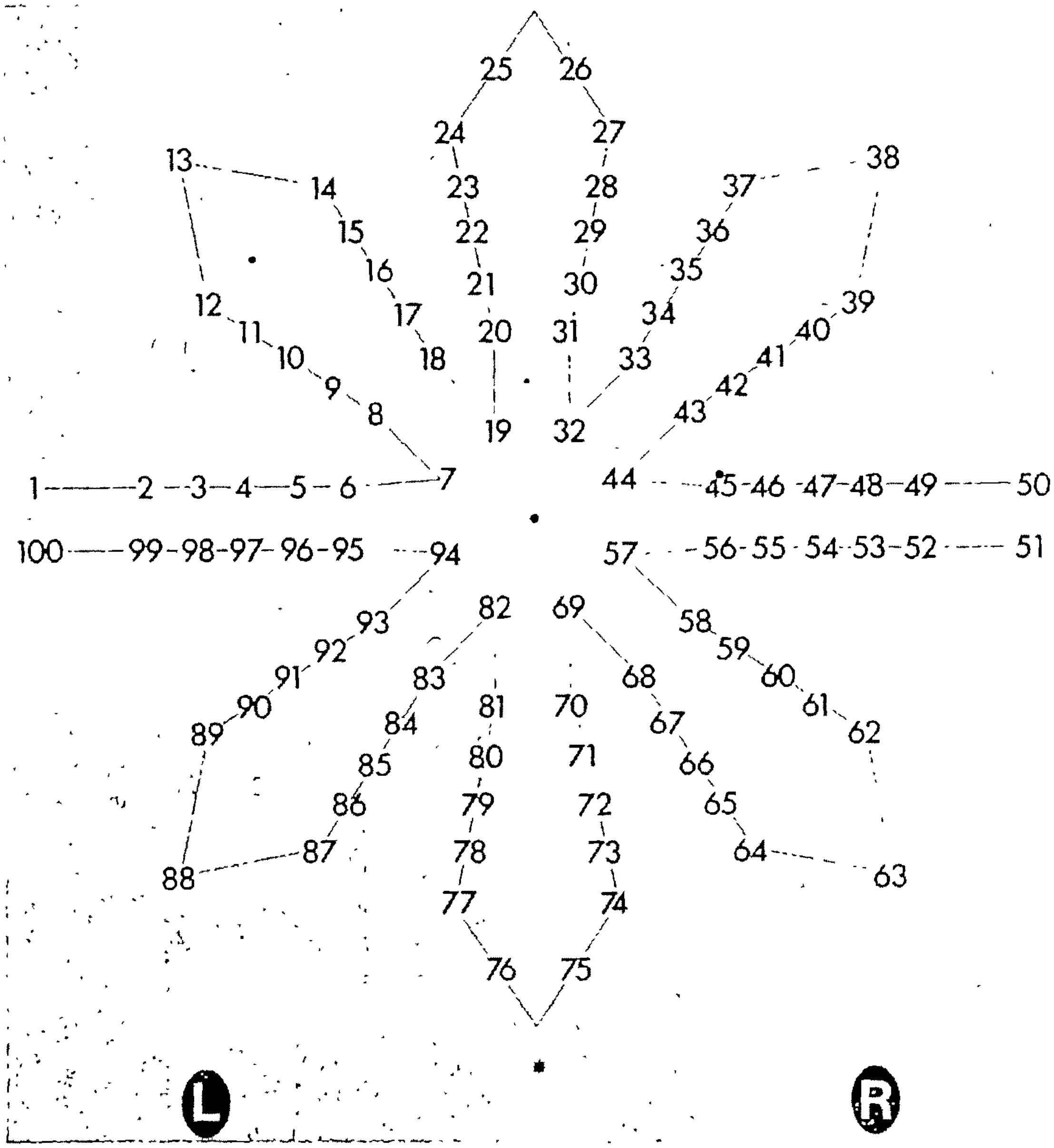

Fig. 1 *Oculokinetic visual field test chart. The reader can perform the test (albeit with difficulty because this modified chart is half the size of the real test chart) by holding this page 15 cm from the eye and using the appropriate reading correction.*

areas of the visual field from 5 to 25°. The numbers associated with disappearance of the central test stimulus are noted directly on the record sheet by crossing out the respective number. If a unilateral central scotoma is present, the subject is advised to look at each number with the other eye and then to cover that eye to determine whether the test stimulus can be seen by the affected eye. The results recorded by the subject can subsequently be evaluated by a qualified observer. The completed record sheet must be inverted before the results can be compared with visual fields plotted by conventional techniques. As in all visual field tests, the blind spot is a useful guide to the validity of the examination.

METHODS

Over 30 patients attending the Tennent Institute and a peripheral hospital who were known to have visual field defects and 30 healthy volunteers were tested by oculokinetic perimetry. In most cases the examination was performed with the assistance of an optician or a nurse. A few patients had the test chart mailed to their homes, and the results were also returned by mail.

All subjects were encouraged to take their time, to recheck any areas they were unsure of, and to take a break whenever they felt this was required. The results were subsequently assessed in relation to records obtained by opticians using conventional methods.

Results

The majority of persons invited to carry out oculokinetic perimetry understood what was required of them and were able to complete the examination provided the numbers could be read with one eye.

Three out of 33 patients who seemed to carry out the procedure correctly produced false negative results with oculokinetic perimetry. In these three cases a visual field defect was detected only with the Oculus Tubinger perimeter by using a white target of size 1·0 and a filter setting of 10 (which is approximately equivalent to a Goldmann target size of 1–2e). Good topographic correspondence was obtained in 25 out of the remaining 30 cases (Figs. 2A, B).

Five out of 30 healthy controls missed one or both blind spots. Ten of the remaining 25 persons missed the test stimulus at one or more points when it was situated more than 17·5° from fixation. Although an additional seven persons missed the test stimulus within the central 17·5° of vision, only four of these produced a false positive result. Surprisingly two of these four subjects also produced a positive result with the Tubinger perimeter, one being found to have a congenital abnormality of the optic discs. One subject had attempted to read the numbers while looking at the central target.

Some patients were disturbed by the reading segment in their bifocal spectacles. It is interesting that one patient who had previously been tested by conventional methods became aware of her extensive visual field defect only when she carried out oculokinetic perimetry. Some persons asked if they could obtain disposable visual field test charts to enable them or members of their family to test themselves at home. When a patient with serpiginous choroiditis was informed that this was not possible without her consultant's permission, she immediately decided to draw her own test chart.

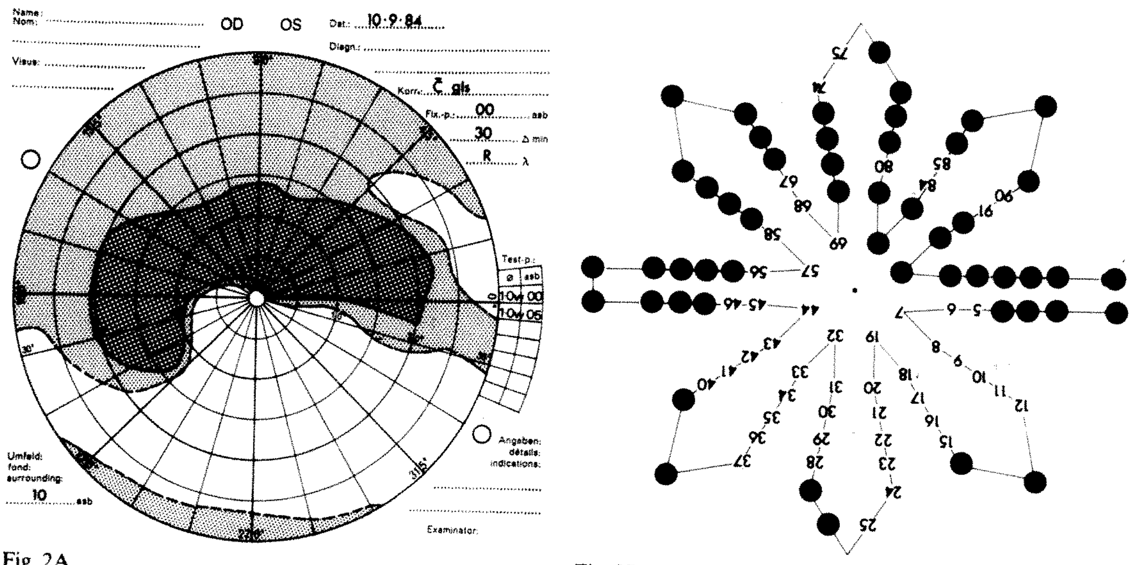

Fig. 2A

Fig. 2B

Fig. 2 *The right central visual field of a 71-year-old female patient with primary open-angle glaucoma plotted* (A) *with the Tubinger perimeter and* (B) *by oculokinetic perimetry. A disposable test chart was mailed to the patient's home, and the completed record sheet was returned a week later.*

Discussion

By moving the eye instead of the test stimulus it is possible for an unsupervised person to carry out self-assessment of the visual fields using only a paper test chart, a record sheet, and a pencil. This method, entitled 'oculokinetic perimetry', might facilitate the detection and management of glaucoma, especially in situations where conventional perimetry is not possible. Susceptible individuals who cannot receive adequate supervision because they live in remote areas could use disposable test charts to perform

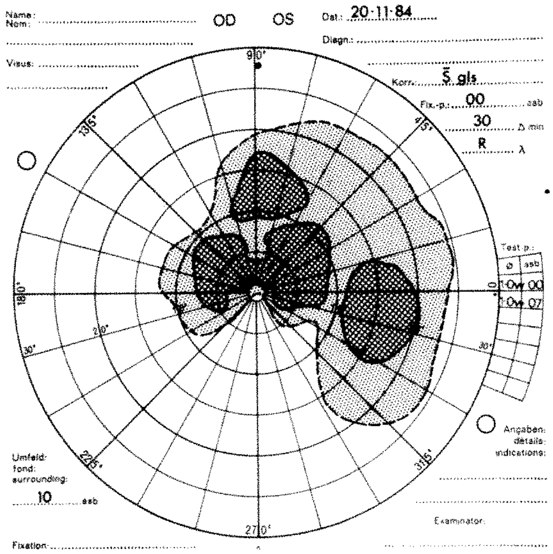

Fig. 3A

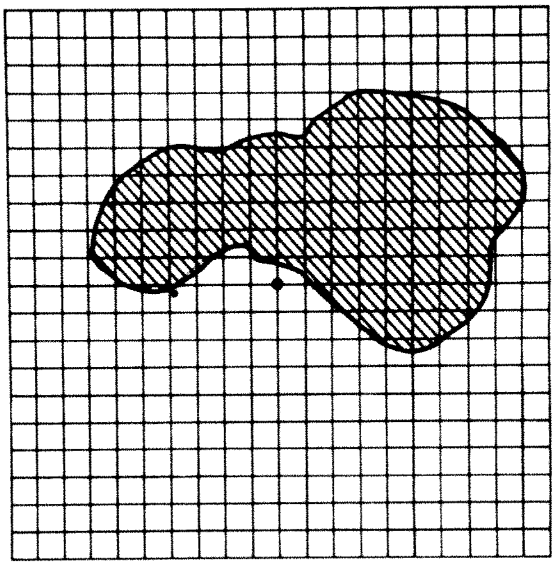

Fig. 3B

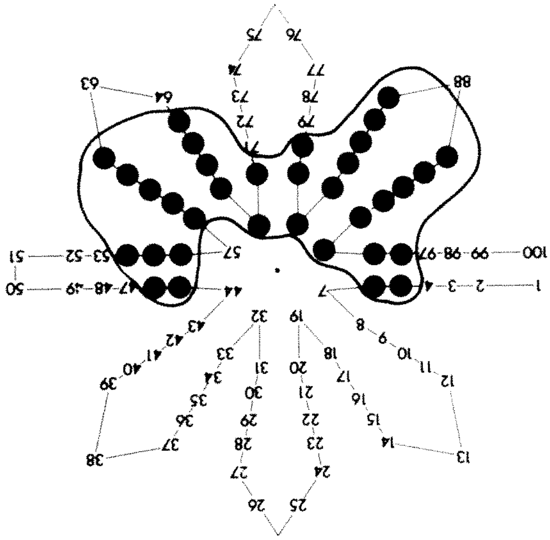

Fig. 3C

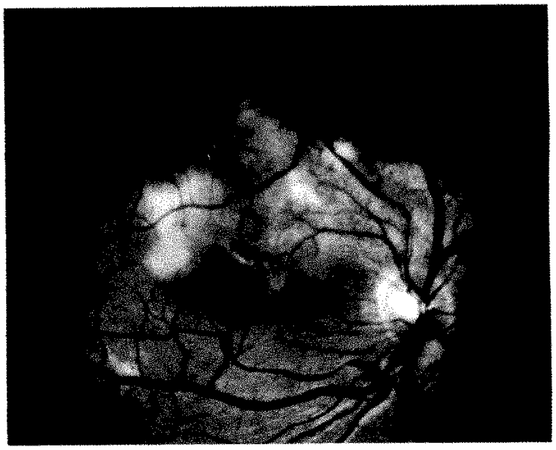

Fig. 3D

Fig. 3 *The right central visual field of a 48-year-old female suffering from serpiginous choroiditis plotted* (A) *with the Tubinger perimeter,* (B) *by means of the Amsler chart, and* (C) *by oculokinetic perimetry. The last test was performed with the patient standing and the chart at knee level, and an adhesive red disc was used as the test stimulus.* (D) *A black and white photograph of the right fundus which has been inverted and reversed to facilitate comparison with the plotted visual fields.*

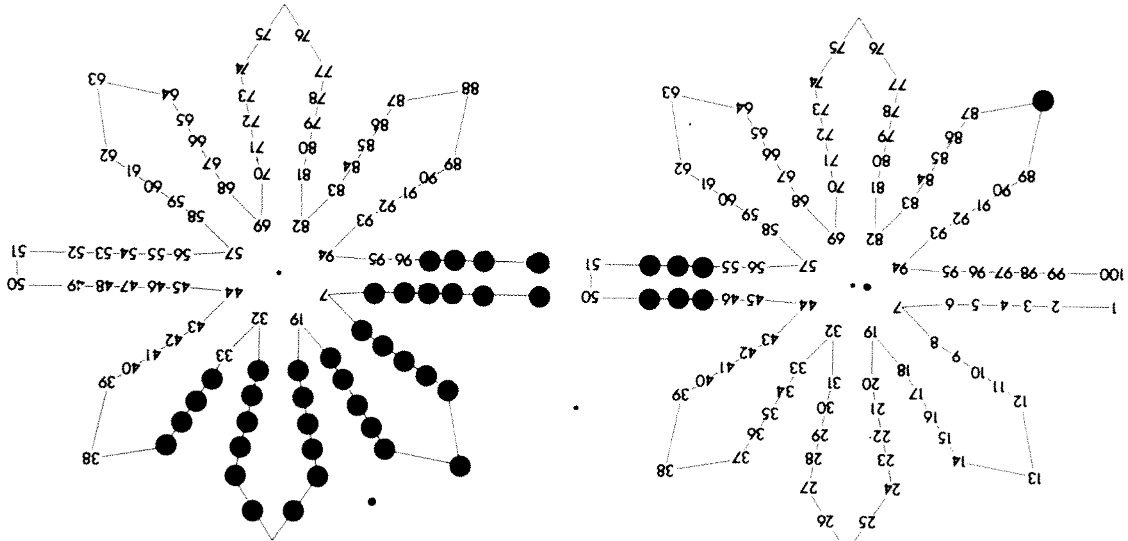

Fig. 4A

Fig. 4B

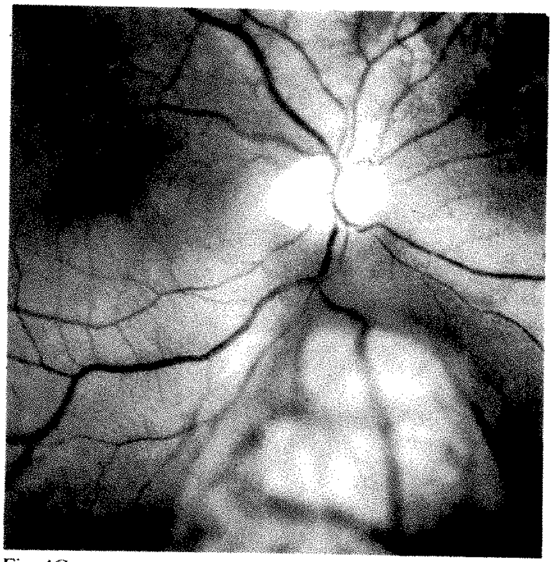

Fig. 4C

Fig. 4 *The central visual fields of a 46-year-old female plotted by oculokinetic perimetry to show (A) an inferotemporal defect in the right eye and (B) a normal visual field in the left eye. (C) a black and white fundus photograph of the right eye, showing a superonasal choroidal melanoma, which has been inverted and reversed to facilitate comparison with the plotted visual field.*

periodic self-assessment at home with the assistance of a friend or relative if necessary. Larger and more convenient oculokinetic visual field test charts would enable non-ophthalmic health care workers to participate in screening programmes for glaucoma, especially in underdeveloped countries. It must be emphasised that the use of this test as a convenient substitute for more reliable conventional perimetry is not recommended.

Oculokinetic perimetry could be of benefit to patients whose vision is threatened by other diseases as well as glaucoma (Figs. 3A, B, C, D, and 4A, B, C). For maximum efficiency special charts would have to be designed for each specific purpose. In areas where innumeracy might be common the test would have to be modified so that the subject's gaze was directed across the chart by means of a series of arrows instead of numbers.

Research is still in progress and it is hoped that results will eventually be published demonstrating the precise scope of oculokinetic perimetry and the most efficient means of its deployment.

I am grateful to Professor W S Foulds, Dr J L Jay, Dr D Allan, Dr G N Dutton, Dr S B Murray, and Miss E McClure for their helpful advice; Mrs A Currie and the Medical Illustration Department for the art work; Miss A McFadden for secretarial assistance; and to the opticians, nurses, and volunteers who carried out the test. The Visual Research Trust, Glasgow, funded the study.

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British Journal of Ophthalmology, 1985, **69**, 932

Correspondence

Posterior chamber lens implantation

SIR, I wish to make two points following recent articles by Percival[1] and Jay[2] concerning posterior chamber intraocular lens implantation associated with filtration surgery. My first point concerns the risk of visual loss in the postoperative period. It would appear that glaucoma patients are at risk of the damaged optic nerve being further compromised from postoperative hypertension following cataract surgery even if the intraocular pressure was controlled with medicines preoperatively. For such eyes the provision of a 'blow off valve' should always be considered, and the presence of an intraocular lens is not a contraindication.

The second point concerns the worry that endothelial damage may follow the occurrence of flat chambers in eyes with a posterior chamber lens. If, as seems likely, these follow excessive drainage through the bleb or along non-conventional outflow pathways, it may be possible to avoid the former by correct suturing of the lamellar scleral flap and the latter by avoiding intraocular lens implantation in eyes severely damaged from glaucoma.

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High Holborn,
London WC1V 7AN

ROGER A HITCHINGS

References

1 Percival SPB. Glaucoma triple procedure of extracapsular cataract extraction, posterior chamber lens implantation, and trabeculectomy *Br J Ophthalmol* 1985, **69**: 99–102

2 Jay JL. Extracapsular lens extraction and posterior chamber intraocular lens insertion combined with trabeculectomy *Br J Ophthalmol* 1985, **69**: 487–90

SIR, Postoperative ocular hypertension may indeed act adversely on an already compromised optic nerve However, it is a recognised complication of any intraocular surgery including trabeculectomy and laser trabeculoplasty. It is transient and, if watched for, should not rise to dangerous or unmanageable levels. The use of Healonid during the glaucoma triple procedure may enhance this complication but tends to obviate the more serious risk of shallow or flat anterior chamber and possible macular oedema associated with hypotony

Concerning the contraindication to lens implantation, experience has shown that, using the technique recommended,[1] flat chambers seldom arise The capsule supported posterior chamber lens once in position is unlikely to compromise the corneal endothelium or optic nerve either directly or indirectly. Thus severe glaucoma is not necessarily a contraindication to its use.

Scarborough Hospital,
Scarborough,
North Yorkshire,
YO12 6QL

S P B PERCIVAL

Reference

1 Glaucoma triple procedure of extracapsular cataract extraction, posterior chamber lens implantation, and trabeculectomy *Br J Ophthalmol* 1985; **69**: 99–102.

SIR, In his letter Mr Hitchings mentions firstly the risk of a postoperative rise in intraocular pressure in glaucoma patients following cataract surgery. This problem seems less likely where trabeculectomy has been combined with the cataract extraction and is one of the reasons why many surgeons favour a combined operation.

His second point is more directly relevant to my own paper [1] He seems concerned about the risk of a postoperative flat anterior chamber in the presence of a posterior chamber intraocular lens following combined surgery. I may best answer this point by quoting from the summary of my paper. 'In addition the anterior chamber cannot become shallow, as the rigid legs of this lens [Rayner Pearce tripod] extend behind the iris beyond the periphery of the cornea and prevent forward movement of the implant even if there is excessively free drainage of aqueous after the operation ' This fail-safe feature of the Pearce tripod lens is explained in the discussion section and illustrated in Fig. 3

Western Infirmary,
Glasgow G11 6NT

JEFFREY L JAY

Reference

1 Jay JL Extracapsular lens extraction and posterior chamber intraocular lens insertion combined with trabeculectomy *Br J Ophthalmol* 1985, **69**: 487–90

Book review

Contemporary Issues in Ophthalmology. Vol 1. **Herpes Simplex Infections of the Eye.** Edited by Frederick C Blodi. Pp 171. £37·00 Churchill Livingstone: Edinburgh. 1984.

This short volume has chapters by several authors covering some important topics on herpes simplex infections of the eye The first and last chapters are particularly useful, giving concise and contemporary analysis of the eye disease and management. My only criticism is that I would have expected more basic science as far as the virus itself was concerned and the antiviral agents used Apart from this I found the book very readable, interesting, and informative. Priced at £37, it is within the grasp of most ophthalmologists

RONALD J MARSH

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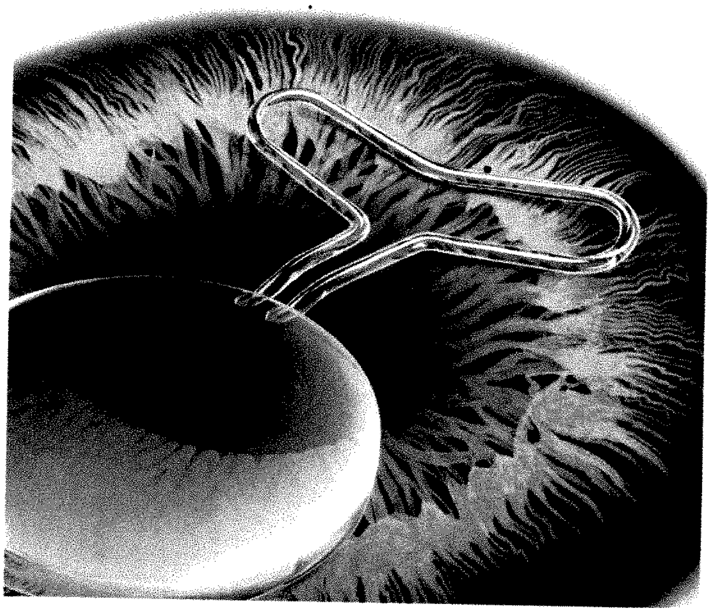

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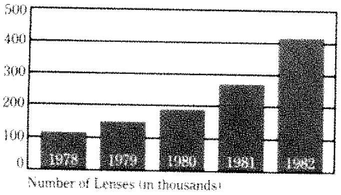

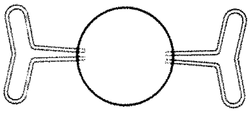

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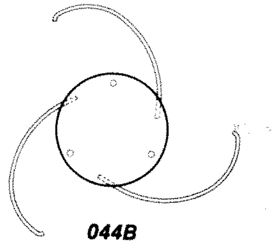

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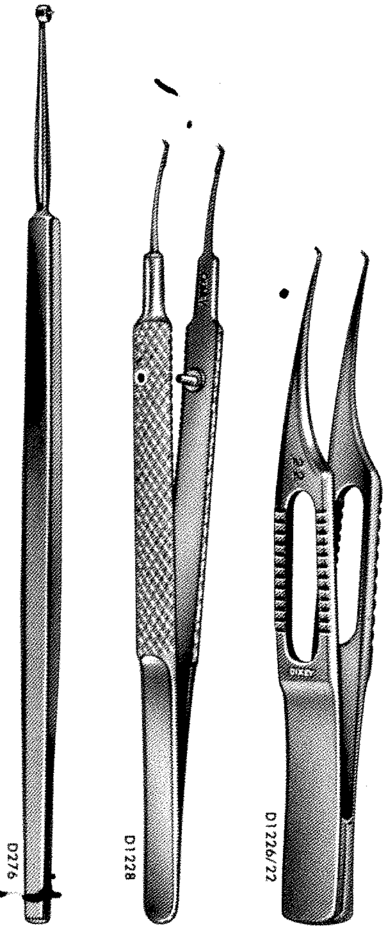

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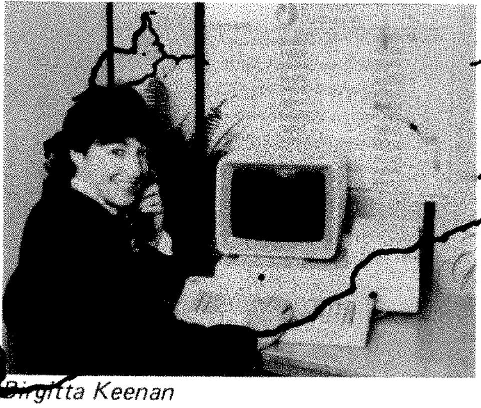

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